

77 Rec'd PCT/PTO 26 NOV 2001

FORM PT0-1390 (Rev. 1/98) (adapted)

U.S. DEPARTMENT OF COMMERCE — PATENT AND TRADEMARK OFFICE		ATTORNEY DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ABR 022 US
INTERNATIONAL APPL'N NO.	INTERNATIONAL FILING DATE	US Appl'n No. (if known, 37 CFR 1.5)
PCT/SE00/01079	26 MAY 2000	09/926596
		PRIORITY DATE CLAIMED
		28 MAY 1999

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2)).
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3)).
 - a. ☒ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventors (unexecuted) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 18. below concern document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
 ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Formal drawings
17. ☒ Return receipt transmittal (MPEP §503) (specifically itemized).
18. ☐ Other items of information:

U.S. APPL'N NO. (if known, 37 CFR 1.5) 09/926596	INT'L APPL'N NO. PCT/SE00/01079	ATTORNEY DOCKET NO. ABR 022 US
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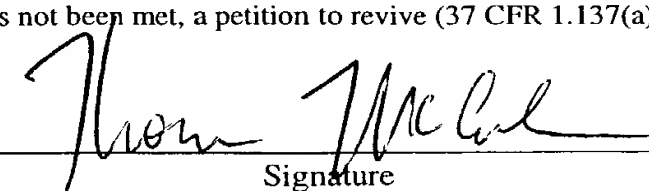
19. <input checked="" type="checkbox"/> The following fees are submitted:				CALCULATIONS		PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(a)(1)-(5):							
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO and international Search Report not prepared by the EPO or JPO				\$1040.00			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but International Search Report prepared by the EPO or JPO				\$890.00			
International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee paid to USPTO (37 CFR 1.445(a)(2))				\$740.00			
International preliminary examination fee (37 CFR 1.482) paid to USPTO but all claims did not satisfy provisions of PCT Article 33(1)-(4)				\$710.00			
International preliminary examination fee (37 CFR 1.482) paid to USPTO and all claims satisfied provisions of PCT Article 33(1)-(4)				\$100.00			
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$ 1,040.00			
Surcharge of \$130.00 for furnishing oath or declaration later than <input type="checkbox"/> 20 <input checked="" type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$ 130.00			
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE				
Total claims	18 - 20 =	0	x \$18.00	\$			
Ind. claims	12 - 3 =	9	x \$84.00	\$ 756.00			
MULTIPLE DEPENDENT CLAIM(s) (if applicable)			+ \$280.00	\$			
TOTAL OF ABOVE CALCULATIONS =				\$			
Reduction of 1/2 for filing by small entity, if applicable. A Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) -				\$			
SUBTOTAL =				\$ 1,926.00			
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f)).				\$			
TOTAL NATIONAL FEE =				\$ 1,926.00			
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). \$40.00 per property +				\$			
TOTAL FEES ENCLOSED =				\$ 1,926.00			
Amount to be:				refunded:		\$	
				charged:		\$	

- a. ☐ A check in the amount of \$ _____ to cover the above fees is enclosed.
- b. ☒ Please charge my Deposit Acct. No. 50-0828 (PowderJect Tech.) in the amount of \$ 1,926.00 to cover the above fees.
- c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Acct. No. 50-0828 (PowderJect Tech.).

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

Thomas P. McCracken
PowderJect Technologies, Inc.
6511 Dumbarton Circle
Fremont, CA 94555


Signature
Thomas P. McCracken, Reg. No. 38,548
Tel. 510-742-9700, ext. 209
Fax 510-742-9720

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08 JUL 2002

7b3

Patent

Attorney's Docket No. 033267-011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Anders FOLKESSON et al

Application No.: 09/926,596

Filed: November 26, 2001

For: FIMBRIAL PROTEINS



)
)
) Group Art Unit:

)
) Examiner:

)
) Confirmation No.: 6671

SUPPLEMENTAL PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Further to the Preliminary Amendment filed on November 26, 2001, and in response to the Notification of Missing Requirements Under 35 U.S.C. 371 mailed on January 7, 2002, please amend the above-identified application as follows:

IN THE SPECIFICATION:

In compliance with 37 C.F.R. § 1.823(a), please substitute the attached paper copy of the Sequence Listing for the originally filed Sequence Listing on pages 14-66 of the application.

Please replace the paragraph at page 4, lines 3-9 with the following paragraph:

--Figure 2: Schematic representation of the pTY52 cosmid comprising the *tcf*-operon

SEQ ID NO:6.

A *tcf* specific PCR fragment of 11105 bp was cloned into the Expand vector I cosmid (Roche). The insert is represented with a thick black line while vector sequences are represented with thin lines. Relevant restriction sites sequences are indicated. The position of the *tcf*-operon, i.e. *tcfA*, *B*, *C* and *D* (SEQ ID NO:6) is represented by a shaded arrow.--

Please replace the paragraph at page 4, lines 15-21 with the following paragraph:

--Sequence listing

SEQ ID NO:1 - DNA sequence of the genes encoding the precursor of the saf fimbriae unit of *Salmonella enterica* subspecies I.

SEQ ID NO:6 - DNA sequence of the genes which encode the precursor of the tcf fimbriae unit of *Salmonella enterica* subspecies I serovar Typhi.--

Please replace the paragraph at page 4, lines 23-29 with the following paragraph:

--Deposit information

The phages carrying the inserted SEQ ID NO:1, i.e. phages clones B1, D1, F11 and N10 (see Figure 1) have been given the ECACC Accession numbers 99051922, 99051923, 99051924, and 99051925, respectively.

The cosmid carrying the inserted SEQ ID NO:6, i.e. cosmid pTY52 (see Figure 2) has been given the ECACC Accession number 99051926.--

1. (Amended) A peptide encoded by a nucleotide sequence selected from SEQ ID NO:1 and SEQ ID NO:6 for use in medicine.
2. (Amended) Antibodies directed against a peptide encoded by a nucleotide sequence selected from SEQ ID NO:1 and SEQ ID NO:6 for use in medicine.
3. (Amended) A nucleotide sequence selected from SEQ ID NO:1 and SEQ ID NO:6 for use in medicine.
4. (Amended) A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a peptide encoded by a nucleotide sequence selected from SEQ ID NO:1, or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.
5. (Amended) A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a peptide encoded by a nucleotide sequence selected from SEQ ID NO:6 or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.

6. (Amended) A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a nucleic acid sequence selected from SEQ ID NO:1 and, optionally, a pharmaceutically acceptable carrier.

7. (Amended) A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a nucleic acid sequence selected from SEQ ID NO:6 and, optionally, a pharmaceutically acceptable carrier.

8. (Amended) A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from SEQ ID NO:1, has been inserted and, optionally, a pharmaceutically acceptable carrier.

9. (Amended) A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from SEQ ID NO:6, has been inserted and, optionally, a pharmaceutically acceptable carrier.

10. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 4 to said mammal.

11. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 5 to said mammal.

12. (Amended) Antibodies directed against a peptide encoded by a nucleotide sequence selected from SEQ ID NO:1, and from SEQ ID NO:6, for use in a diagnostic method.

13. (Amended) Peptide encoded by a nucleotide sequence selected from SEQ ID NO:1, and SEQ ID NO:6, for use in a diagnostic method.

14. (Amended) Primers for, or probes that hybridize with, a nucleotide sequence selected from SEQ ID NO:1 and SEQ ID NO:6, for use in a diagnostic method for the purpose of detecting *Salmonella enterica* subspecies I.

15. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 6 to said mammal.

16. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 8 to said mammal.

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17. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 7 to said mammal.

18. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 9 to said mammal.

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REMARKS

Entry of the foregoing and prompt and favorable consideration of the subject application, in light of the following remarks, are respectfully requested.

By the foregoing Supplemental Preliminary Amendment, the specification has been amended to replace the originally filed Sequence Listing with the attached copy of the Sequence Listing, which was filed in parent Application No. PCT/SE00/01079. Although the presently filed Sequence Listing is believed to be contain identical material to combined Sequence Listings 1 and 2 as originally filed with the present specification, this submission is being made in accordance with the statement pursuant to 37 C.F.R. § 1.821(f), which is submitted herewith. No new matter is believed to have been added.

In addition, all references to SEQ ID NO:2 in the specification and claims have been amended to recite "SEQ ID NO:6". The basis for this amendment is the following: The specification as originally filed was filed with two sequence listings, Sequence Listing No. 1, containing SEQ I NOS:1-5, and Sequence Listing No. 2, containing an additional SEQ ID NOS:1-6 (i.e., which were not duplicative of SEQ ID NOS:1-5 of Sequence Listing No. 1).

In the application as filed, sequence number 1 of Sequence Listing number 2 was referred to as SEQ ID NO 2. That only sequence no. 1 of Sequence Listing no. 2 could have been intended by this indication is clear from a comparison of *page 4, line 4* of the description, where SEQ ID NO 2 is identified as the tcf-operon, versus the information given on *page 36 of the Sequence Listing part under items <223>* referring to sequence no. 1 of Sequence Listing no. 2. Namely, under these items, it is stated that the sequence

no. 1 of Sequence Listing no. 2 is the nucleic sequence of the tcf A, B, C and D putative fimbrial subunits respectively and of the tinR putative transcriptional regulator, i.e., is the sequence of the tcf operon. Therefore, it would have been obvious to anyone studying the application as filed that SEQ ID NO:2 referred to sequence no. 1 of Sequence Listing no. 2. Due to renumbering of the sequences, as indicated herein above, this is now sequence number 6, and should consequently be referred to as SEQ ID NO:6.

To further demonstrate that only this sequence could have been intended, it may be noted that in Sequence Listing no. 2 of the application as filed, only the first sequence was a nucleotide acid sequence, the others being protein sequences.

Moreover, on page 4, lines 16-21, the sequences referred to are DNA sequences. The only DNA sequences appearing in the sequence listing part are present SEQ ID NO:1 and SEQ ID NO:6, since all the other sequences are protein sequences. A comparison of the description of the two sequences on page 4, lines 16-21 versus the entries made under items <223> on page 1 and 36, respectively of the Sequence Listing part clearly shows that the sequence described on page 4, lines 16-18 is SEQ ID NO:1 and the sequence described on page 4, lines 19-21 is SEQ ID NO:6.

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In the event that there are any questions relating to this Supplemental Preliminary Amendment, or the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: Sharon E. Crane
Sharon E. Crane, Ph.D.
Registration No. 36,113

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: July 8, 2002

Attachment to Supplemental Preliminary Amendment filed July 8, 2002

Mark-up of Specification

Paragraph at page 4, lines 3-9

Figure 2: Schematic representation of the pTY52 cosmid comprising the *tcf*-operon
 [(SEQ ID NO 2)] SEQ ID NO:6.

A *tcf* specific PCR fragment of 11105 bp was cloned into the Expand vector I cosmid (Roche). The insert is represented with a thick black line while vector sequences are represented with thin lines. Relevant restriction sites sequences are indicated. The position of the *tcf*-operon, i.e. *tcfA*, *B*, *C* and *D* [(SEQ ID NO 2)] (SEQ ID NO:6) is represented by a shaded arrow.

Paragraph at page 4, lines 15-21

Sequence listing

[(SEQ ID NO 1)] SEQ ID NO:1 - DNA sequence of the genes encoding the precursor of the saf fimbriae unit of *Salmonella enterica* subspecies I.

[(SEQ ID NO 2)] SEQ ID NO:6 - DNA sequence of the genes which encode the precursor of the tcf fimbriae unit of *Salmonella enterica* subspecies I serovar Typhi.

Paragraph at page 4, lines 23-29

Deposit information

The phages carrying the inserted [(SEQ ID NO 1)] SEQ ID NO:1, i.e. phages clones B1, D1, F11 and N10 (see Figure 1) have been given the ECACC Accession numbers 99051922, 99051923, 99051924, and 99051925, respectively.

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The cosmide carrying the inserted [SEQ ID NO 2] SEQ ID NO:6, i.e. cosmide pTY52 (see Figure 2) has been given the ECACC Accession number 99051926.



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Attachment to Supplemental Preliminary Amendment filed July 8, 2002

Mark-up of Claims

1. (Amended) [Peptide] A peptide encoded by a nucleotide sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1 and [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6 for use in medicine.

2. (Amended) Antibodies directed against a peptide encoded by a nucleotide sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1 and [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6 for use in medicine.

3. (Amended) [Nucleotide] A nucleotide sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1 and [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6 for use in medicine.

4. (Amended) A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a peptide encoded by a nucleotide sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1, or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.

5. (Amended) A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a peptide encoded by a nucleotide sequence selected from [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6 or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.

Attachment to Supplemental Preliminary Amendment filed July 8, 2002

6. (Amended) A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a nucleic acid sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1 and, optionally, a pharmaceutically acceptable carrier.

7. (Amended) A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a nucleic acid sequence selected from [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6 and, optionally, a pharmaceutically acceptable carrier.

8. (Amended) A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1, has been inserted and, optionally, a pharmaceutically acceptable carrier.

9. (Amended) A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6, has been inserted and, optionally, a pharmaceutically acceptable carrier.

Attachment to Supplemental Preliminary Amendment filed July 8, 2002

10. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 4 to said mammal.
11. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 5 to said mammal.
12. (Amended) Antibodies directed against a peptide encoded by a nucleotide sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1, and from [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6, for use in a diagnostic method.
13. (Amended) Peptide encoded by a nucleotide sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1, and [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6, for use in a diagnostic method.
14. (Amended) Primers for, or probes that hybridize with, a nucleotide sequence selected from [Sequence Listing No. 1 (SEQ ID NO 1)] SEQ ID NO:1 and [Sequence Listing No. 2 (SEQ ID NO 2)] SEQ ID NO:6, for use in a diagnostic method for the purpose of detecting *Salmonella enterica* subspecies I.

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15. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 6 to said mammal.

16. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 8 to said mammal.

17. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 7 to said mammal.

18. A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 9 to said mammal.



Patent

Attorney's Docket No. 033267-011

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of) BOX: SEQUENCE
Anders FOLKESSON et al.)
Application Serial No.: 09/926,596)
Filed: November 26, 2001) Group Art Unit:
For: FIMBRIAL PROTEINS) Examiner:
) Confirmation No.: 6671

DECLARATION PURSUANT TO
37 C.F.R. §§ 1.821-.825

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

I, Sharon E. Crane, declare as follows:

1. That the content of the paper copy of the sequence listing and the computer readable copy of the sequence listing submitted in accordance with 37 C.F.R. § 1.821(c) and (e), respectively, are the same in compliance with 37 C.F.R. §§ 1.821(f).
2. That the submission, filed in accordance with 37 C.F.R. §§ 1.821(g)[or (h)] & 1.825(a), herein does not include new matter [or go beyond the disclosure in the international application].

I hereby declare that all statements made herein of my own knowledge are true and that all statements were made on information and belief and are believed to be true; and

Declaration Pursuant to 37 C.F.R. §§ 1.821-.825

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further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued.

July 8, 2002

Date



Sharon E. Crane, Ph.D.

Reg. No. 36,113



PTO/PCT Rec'd

08 JUL 2002

SEQUENCE LISTING

<110> FOLKESSON, Anders; NORMARK, Staffan; LÖFDAHL, Sven

<120> Fimbrial proteins

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Ser Ala Arg Thr Thr Gln Thr Asp Tyr Lys Met Asp Met Val Gly Arg	
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Met Tyr Gly Leu Pro Trp Asn Leu Thr Ala Tyr Gly Gly Ile Gln Ser	
790 795 800 805	

$$\frac{1}{\Gamma(\alpha)} \int_0^t (t-\tau)^{\alpha-1} f(\tau) d\tau = I^\alpha f(t), \quad t \in [0, T],$$

[illegible]

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 ctgttacagc atattttgca ccgataacctg cgcgccaggc aaagttattt tttgaagcag 45255
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 caagtgcctg ggcgagatct tgttgtagct gttgacgctg ttctggtgtt aagactttgc 46155

$\frac{1}{2} \left(\frac{1}{2} + \frac{1}{2} \right) = \frac{1}{2}$

<400> 4

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1 5 10 15

His Cys Ala Asn Ala His Thr Tyr Thr Phe Asp Ala Ser Met Leu Gly
20 25 30

Asp Ala Ala Lys Gly Val Asp Met Ser Leu Phe Asn Gln Gly Leu Gln
35 40 45

Gln Pro Gly Thr Tyr Arg Val Asp Val Met Val Asn Gly Lys Arg Val
50 55 60

Asp Thr Arg Asp Val Val Phe Lys Leu Glu Lys Asp Gly Gln Gly Thr
65 70 75 80

Pro Val Leu Ala Pro Cys Leu Thr Val Ser Gln Leu Ser Arg Tyr Gly
85 90 95

Val Lys Thr Glu Asp Tyr Pro Gln Leu Trp Lys Ala Ala Lys Pro Pro
100 105 110

Asp Glu Cys Ala Asp Leu Thr Ala Ile Pro Gln Ala Lys Ala Val Leu
115 120 125

Asp Ile Asn Asn Gln Gln Leu Gln Leu Ser Ile Pro Gln Leu Ala Leu
130 135 140

Arg Pro Glu Phe Lys Gly Ile Ala Pro Glu Asp Leu Trp Asp Asp Gly
145 150 155 160

Ile Pro Ala Phe Leu Met Asn Tyr Ser Ala Arg Thr Thr Gln Thr Asp
165 170 175

Tyr Lys Met Asp Met Val Gly Arg Asp Asn Ser Ser Trp Val Gln Leu
180 185 190

Gln Pro Gly Ile Asn Ile Gly Ala Trp Arg Val Arg Asn Ala Thr Ser
195 200 205

Trp Gln Arg Ser Ser Gln Leu Ser Gly Lys Trp Gln Ala Ala Tyr Thr
210 215 220

Tyr Ala Glu Arg Gly Leu Tyr Ser Leu Lys Ser Arg Leu Thr Leu Gly
225 230 235 240

Gln Lys Thr Ser Gln Gly Glu Ile Phe Asp Ser Val Pro Phe Thr Gly
245 250 255

Val Met Leu Ala Ser Asp Asp Asn Met Val Pro Tyr Ser Glu Arg Gln
260 265 270

Phe Ala Pro Val Val Arg Gly Ile Ala Arg Thr Gln Ala Arg Val Glu
275 280 285

$$\frac{1}{2} \left(\frac{1}{2} + \frac{1}{2} \right) = \frac{1}{2} \cdot 1 = \frac{1}{2}$$

Asn Ser Ala Leu His Leu Ala Trp Asn Gly Asp Tyr Gly Leu Leu Gly
625 630 635 640

Gly Asp Tyr Ser Tyr Ser Arg Ala Met Arg Gln Met Gly Val Asn Ile
645 650 655

Ala Gly Gly Ile Val Ile His His His Gly Val Thr Leu Gly Gln Pro
660 665 670

Leu Gln Gly Ser Val Ala Leu Val Glu Ala Pro Gly Ala Ser Gly Val
675 680 685

Pro Val Gly Gly Trp Pro Gly Val Lys Thr Asp Phe Arg Gly Asp Thr
690 695 700

Thr Val Gly Asn Leu Asn Val Tyr Gln Glu Asn Thr Val Ser Leu Asp
705 710 715 720

Pro Ser Arg Leu Pro Asp Asp Ala Glu Val Thr Gln Thr Asp Val Arg
725 730 735

Val	Val	Pro	Thr	Glu	Gly	Ala	Val	Val	Glu	Ala	Lys	Phe	His	Thr	Arg
			740					745					750		

Ile Gly Ala Arg Ala Leu Met Thr Leu Lys Arg Glu Asp Gly Ser Ala
755 760 765

Ile Pro Phe Gly Ala Gln Val Thr Val Asn Gly Gln Asp Gly Ser Ala
770 775 780

Ala Leu Val Asp Thr Asp Ser Gln Val Tyr Leu Thr Gly Leu Ala Asp
785 790 795 800

Lys Gly Glu Leu Thr Val Lys Trp Gly Ala Gln Gln Cys Arg Val Asn
805 810 815

Tyr Arg Leu Pro Ala His Lys Gly Ile Ala Gly Leu Tyr Gln Met Ser
820 825 830

Gly Leu Cys Arg
835

<210> 5

<211> 156

<212> PRT

<213> Salmonella typhimurium

<400> 5

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Leu Leu Val Ala Ala Ser Ser Leu Val Pro Ile Ala Asn Ala Ala Glu
20 25 30

Lys Leu Gln Thr Thr Leu Arg Val Gly Thr Tyr Phe Arg Ala Gly His
35 40 45

Val Pro Asp Gly Met Val Leu Ala Gln Gly Trp Val Thr Tyr His Gly
 50 55 60

Ser His Ser Gly Phe Arg Val Trp Ser Asp Glu Gln Lys Ala Gly Asn
 65 70 75 80

Thr Pro Thr Val Leu Leu Leu Ser Gly Gln Gln Asp Pro Arg His His
 85 90 95

Ile Gln Val Arg Leu Glu Gly Glu Gly Trp Gln Pro Asp Thr Val Ser
 100 105 110

Gly Arg Gly Ala Ile Leu Arg Thr Ala Ala Asp Asn Ala Ser Phe Ser
 115 120 125

Val Val Val Asp Gly Asn Gln Glu Val Pro Ala Asp Thr Trp Thr Leu
 130 135 140

Asp Phe Lys Ala Cys Ala Leu Ala Gln Glu Asp Thr
 145 150 155

<210> 6
 <211> 9253
 <212> DNA
 <213> Salmonella typhi

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<220>
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 <223> tinR putative transcriptional regulator

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gattagatca gttgaatccg gacggactgt taaagatgtc taccgggagg ccggtatttc 180
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aacatctctc cccagtctgc gaagcctttg tttgacgtca ggataatgct cgctttttca 540
taccgtcggg tcagcagtcg gaagaacaga ctggcttcct cactgggcat tggcaggtaa 600
cctatttcgt ccaggatcag ccccccgcga tagctcagtt gttgtagctg gcgctccagg 660
cggttttcca gcttcgcttt catcagcgtc taccaacctg tctgcgggca tgaacaacac 720
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ttctattcct gctgcagcgc catgcacagg aatgtcgact tattttgggc tgacagaggc 1020
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gtaaacaaca ttgacaggta agggactggc atcaatttga atgggtatttt ttataacatt 1140
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gaaaaaaaca gaggtattga gcgaaaaatt ttattccgta tgatgccctc cacacaaaat 1800
gtattaacac tgaatcgtaa tttgcttctt tatgctgata actttctgtc tatgctaata 1860
ctaaaatttagatgactttt atacggtaaa atctgggt atg aat ttt aaa gat act 1915
Met Asn Phe Lys Asp Thr

1

5

ctt ccc ggg gtg ttt ctc tgt gtc gct atg ttt gca tgt ggt cat gcc	1963
Leu Pro Gly Val Phe Leu Cys Val Ala Met Phe Ala Cys Gly His Ala	
10 15 20	
agg gcg aat atg ctc gtt tat ccc atg gcg gca gaa att aat agt agc	2011
Arg Ala Asn Met Leu Val Tyr Pro Met Ala Ala Glu Ile Asn Ser Ser	
25 30 35	
cgc gaa gag gcc acc tcg ctg ttc gtc tat tct aaa tca gat cat gtg	2059
Arg Glu Glu Ala Thr Ser Leu Phe Val Tyr Ser Lys Ser Asp His Val	
40 45 50	
caa tat att cga aca aga atc atg cgt att gaa cac ccc ggt atg cca	2107
Gln Tyr Ile Arg Thr Arg Ile Met Arg Ile Glu His Pro Gly Met Pro	
55 60 65 70	
cag gag aag gag gta cca gca ggg aat gat ata gag aca gga ctt gtt	2155
Gln Glu Lys Glu Val Pro Ala Gly Asn Asp Ile Glu Thr Gly Leu Val	
75 80 85	
gtc tcc ccg gag aaa ttt gct ctt tcc ccg gga aca aaa aaa aca ata	2203
Val Ser Pro Glu Lys Phe Ala Leu Ser Pro Gly Thr Lys Lys Thr Ile	
90 95 100	
cgt gtt atc agt act cag gca ccg gaa aga gag gaa gcc tgg cgg gta	2251
Arg Val Ile Ser Thr Gln Ala Pro Glu Arg Glu Glu Ala Trp Arg Val	
105 110 115	
tac ttc gag gct gtt cct gaa ctg gaa gat gat cca cag gca ggc gga	2299
Tyr Phe Glu Ala Val Pro Glu Leu Glu Asp Asp Pro Gln Ala Gly Gly	
120 125 130	
aag caa aat tca tcc gta agt gtg aat ctt gtc tgg ggg gtg ttg ctg	2347
Lys Gln Asn Ser Ser Val Ser Val Asn Leu Val Trp Gly Val Leu Leu	
135 140 145 150	
cgt gtt tct ccg tca gac ccc agg cct gcg ctg gta acg gac ggt cac	2395
Arg Val Ser Pro Ser Asp Pro Arg Pro Ala Leu Val Thr Asp Gly His	
155 160 165	
cac ctg ctg aat acg gga aac aca cgg ctt tct ctt att cgg gct ggc	2443
His Leu Leu Asn Thr Gly Asn Thr Arg Leu Ser Leu Ile Arg Ala Gly	
170 175 180	
aac tgc gac acc aca tgc cac tgg cag aat ata ggc aaa agt att tat	2491
Asn Cys Asp Thr Thr Cys His Trp Gln Asn Ile Gly Lys Ser Ile Tyr	
185 190 195	
ccc ggc ggg agt gct gat att ccg gcc gga ata aaa agt aat gca ttt	2539
Pro Gly Gly Ser Ala Asp Ile Pro Ala Gly Ile Lys Ser Asn Ala Phe	
200 205 210	
cgt gtg gaa tat cgt acg ggt gca aat tca ccg gta atc tct gct gat	2587
Arg Val Glu Tyr Arg Thr Gly Ala Asn Ser Pro Val Ile Ser Ala Asp	
215 220 225 230	
tta aca gca gcc gga aag taa aaacacacgg agcgtacgct ataccctaca	2638

tctttacgtg agtcggttatt tctgg atg tat tat tta ctg gga ttg tgc agt 3386
Met Tyr Tyr Leu Leu Gly Leu Cys Ser
430 435

$\frac{1}{2} \times \frac{1}{2} = \frac{1}{4}$, $\frac{1}{3} \times \frac{1}{3} = \frac{1}{9}$, $\frac{1}{4} \times \frac{1}{4} = \frac{1}{16}$, $\frac{1}{5} \times \frac{1}{5} = \frac{1}{25}$, $\frac{1}{6} \times \frac{1}{6} = \frac{1}{36}$, $\frac{1}{7} \times \frac{1}{7} = \frac{1}{49}$, $\frac{1}{8} \times \frac{1}{8} = \frac{1}{64}$, $\frac{1}{9} \times \frac{1}{9} = \frac{1}{81}$, $\frac{1}{10} \times \frac{1}{10} = \frac{1}{100}$

Ser Ser Gln Pro Phe Ser Leu Gly Phe Gly Gln Gln Ser Leu Leu Leu	
1145 1150 1155	
atg gaa ggc tat aac gcc acg gag gtg acc att gag gat gca ggg gtt	5594
Met Glu Gly Tyr Asn Ala Thr Glu Val Thr Ile Glu Asp Ala Gly Val	
1160 1165 1170	
agt tca cag ggt atg gca ggc gta aaa gcg gga ggg gga agc agg tgt	5642
Ser Ser Gln Gly Met Ala Gly Val Lys Ala Gly Gly Gly Ser Arg Cys	
1175 1180 1185 1190	
tac ttc ctg aca ccc ggg cat ctg ctg gtt cac aac atc agc gcc agt	5690
Tyr Phe Leu Thr Pro Gly His Leu Leu Val His Asn Ile Ser Ala Ser	
1195 1200 1205	
atg agc cga ctg tac gtt ggc cgc gta ctg gac aag gat ggc aga ccg	5738
Met Ser Arg Leu Tyr Val Gly Arg Val Leu Asp Lys Asp Gly Arg Pro	
1210 1215 1220	
ctg ctg gac gca cag cca ctg aac tat cca ttt ttg tgc ttg gga cct	5786
Leu Leu Asp Ala Gln Pro Leu Asn Tyr Pro Phe Leu Ser Leu Gly Pro	
1225 1230 1235	
tcc ggg cga ttt agc ctg cag agc gag cat aaa gaa tcc agc ctg tgg	5834
Ser Gly Arg Phe Ser Leu Gln Ser Glu His Lys Glu Ser Ser Leu Trp	
1240 1245 1250	
ctg ctg tct aaa aac agg atc ctg cgt tgt ccg atg tca gta cat aaa	5882
Leu Leu Ser Lys Asn Arg Ile Leu Arg Cys Pro Met Ser Val His Lys	
1255 1260 1265 1270	
cgt cgg gat gtt atg cag gta gtg ggt gat gtg cgg tgt gaa tta agt	5930
Arg Arg Asp Val Met Gln Val Val Gly Asp Val Arg Cys Glu Leu Ser	
1275 1280 1285	
gac gtg gat gcc ctg cca cag gcg ttg caa ata tgc ccg cgg gtc atc	5978
Asp Val Asp Ala Leu Pro Gln Ala Leu Gln Ile Ser Pro Arg Val Ile	
1290 1295 1300	
cgt ttg ctg aac gtg gca ggt ttg ctg cgc cat tcc gtt cag gaa gcc	6026
Arg Leu Leu Asn Val Ala Gly Leu Leu Arg His Ser Val Gln Glu Ala	
1305 1310 1315	
tga cgtagagata aaggcgttaa ct atg agt aat aaa atg aag tgg acg agt	6078
Met Ser Asn Lys Met Lys Trp Thr Ser	
1320 1325	
atg aca gcc cat tgg tca gca att att aat ttc atc cga aaa tat gtt	6126
Met Thr Ala His Trp Ser Ala Ile Ile Asn Phe Ile Arg Lys Tyr Val	
1330 1335 1340	
tat cca gca agg ata att gcc atc ctg ctg atg gct ggc gct aca ctg	6174
Tyr Pro Ala Arg Ile Ile Ala Ile Leu Leu Met Ala Gly Ala Thr Leu	
1345 1350 1355 1360	
cca caa gtc gcc gat gcg att acc gtc gac ctg aat tac gac aag aac	6222
Pro Gln Val Ala Asp Ala Ile Thr Val Asp Leu Asn Tyr Asp Lys Asn	
1365 1370 1375	
aat gta gcg gtc atc act cct gtc tgg tcc caa gaa tgg agt gta gca	6270

Asn Val Ala Val Ile Thr Pro Val Trp Ser Gln Glu Trp Ser Val Ala	
1380 1385 1390	
aat gtg ttg ggg gga tgg gta tgt cgt tca aac agg aat gaa aat gag	6318
Asn Val Leu Gly Gly Trp Val Cys Arg Ser Asn Arg Asn Glu Asn Glu	
1395 1400 1405	
ggg gcg tgt gaa gaa aca cat ttg gta tgg tgg tat gct ttt gga gct	6366
Gly Ala Cys Glu Glu Thr His Leu Val Trp Trp Tyr Ala Phe Gly Ala	
1410 1415 1420	
tat tca aaa att cgt ctg cgt ttc aga gaa caa atc agc cat gcc gaa	6414
Tyr Ser Lys Ile Arg Leu Arg Phe Arg Glu Gln Ile Ser His Ala Glu	
1425 1430 1435 1440	
att acg ctc ata ctg ctc ggc agt gtt cgt gat gcc tgt tat act ggt	6462
Ile Thr Leu Ile Leu Leu Gly Ser Val Arg Asp Ala Cys Tyr Thr Gly	
1445 1450 1455	
gtc atc aac atg aac gct gct gca tgt caa tgg ggt agg tgc ctg aaa	6510
Val Ile Asn Met Asn Ala Ala Cys Gln Trp Gly Arg Ser Leu Lys	
1460 1465 1470	
ctt agg ata cct tca gaa gag ctt gcg aag ata cct aca agc gga aca	6558
Leu Arg Ile Pro Ser Glu Glu Leu Ala Lys Ile Pro Thr Ser Gly Thr	
1475 1480 1485	
tgg aaa gca acg tta gtc ctg gat tat tta caa tgg ggc gga gac gat	6606
Trp Lys Ala Thr Leu Val Leu Asp Tyr Leu Gln Trp Gly Gly Asp Asp	
1490 1495 1500	
cct tta ggc aca tca act aca gat atc acg ctg aat gta aca gac cac	6654
Pro Leu Gly Thr Ser Thr Thr Asp Ile Thr Leu Asn Val Thr Asp His	
1505 1510 1515 1520	
ttt gct gaa aat gcg gct att tac ttt ccg caa ttt ggt aca gca acg	6702
Phe Ala Glu Asn Ala Ala Ile Tyr Phe Pro Gln Phe Gly Thr Ala Thr	
1525 1530 1535	
ccc cgg gtg gac ctg aat ctt cac cgg atg aat gcc tca caa atg tgc	6750
Pro Arg Val Asp Leu Asn Leu His Arg Met Asn Ala Ser Gln Met Ser	
1540 1545 1550	
ggc agg gct aat ctg gat atg tgt ctg tat gac gga ggt gtg aaa gcc	6798
Gly Arg Ala Asn Leu Asp Met Cys Leu Tyr Asp Gly Gly Val Lys Ala	
1555 1560 1565	
cgt tca tta cag atg aag ata gaa gga agc aat aag tca ggt acg gga	6846
Arg Ser Leu Gln Met Lys Ile Glu Gly Ser Asn Lys Ser Gly Thr Gly	
1570 1575 1580	
ttt cag gtt ata aag agc gat tct gct gat acg att gat tat gcg gtc	6894
Phe Gln Val Ile Lys Ser Asp Ser Ala Asp Thr Ile Asp Tyr Ala Val	
1585 1590 1595 1600	
agt atg aat tat ggg gga cga agt att cct gtc acc cgt ggc gtg gag	6942
Ser Met Asn Tyr Gly Gly Arg Ser Ile Pro Val Thr Arg Gly Val Glu	
1605 1610 1615	

ttc agt ctg gat aac gtg gat aaa gca gca acg cgt ccg gtg gta ctt 6990
 Phe Ser Leu Asp Asn Val Asp Lys Ala Ala Thr Arg Pro Val Val Leu
 1620 1625 1630

 ccc ggg caa cgg cag gcg gta cgt tgt gtg cca gtg ccc ctt acc ctg 7038
 Pro Gly Gln Arg Gln Ala Val Arg Cys Val Pro Val Pro Leu Thr Leu
 1635 1640 1645

 aca aca caa ccc ttt aac atc aga gag aag cgt tct ggt gag tat cag 7086
 Thr Thr Gln Pro Phe Asn Ile Arg Glu Lys Arg Ser Gly Glu Tyr Gln
 1650 1655 1660

 gga acg ctg aca gtg aca atg ctg atg gga aca caa acc ccc tga 7131
 Gly Thr Leu Thr Val Thr Met Leu Met Gly Thr Gln Thr Pro
 1665 1670 1675

 cagtaattat ttattttatt gatatttttc ttatatgggt ttttaaataca gagttctctt 7191

 tatatacttg ttttatttaa taaagagaat ctattcactt atgaaaataca atgcgtgagg 7251

 ttctgctttc ct atg act gtg tat tta gat gat aaa gat aaa gaa tta ttg 7302
 Met Thr Val Tyr Leu Asp Asp Lys Asp Lys Glu Leu Leu
 1680 1685 1690

 aaa gaa atc caa aaa gat tgt gca caa act tta tgg caa ctt gca tat 7350
 Lys Glu Ile Gln Lys Asp Cys Ala Gln Thr Leu Trp Gln Leu Ala Tyr
 1695 1700 1705

 aaa gtg gga ctt acg ccc aca cca tgt ttc aaa cgt tta aaa aaa ctt 7398
 Lys Val Gly Leu Thr Pro Thr Pro Cys Phe Lys Arg Leu Lys Lys Leu
 1710 1715 1720

 aaa gac agg ggg gtt atc att ggt cag ttc gct tta ttg gat aag gaa 7446
 Lys Asp Arg Gly Val Ile Ile Gly Gln Phe Ala Leu Leu Asp Lys Glu
 1725 1730 1735 1740

 aaa cta ggt ctt tca ctt aat gtc ttt att atg att aac ata tct gag 7494
 Lys Leu Gly Leu Ser Leu Asn Val Phe Ile Met Ile Asn Ile Ser Glu
 1745 1750 1755

 gag caa tac gct agt att tct gag aaa ata aag tca atg cct gag gtt 7542
 Glu Gln Tyr Ala Ser Ile Ser Glu Lys Ile Lys Ser Met Pro Glu Val
 1760 1765 1770

 att gcc ttt tat cga att tct gga tca ttt aat tat tta atg cat aca 7590
 Ile Ala Phe Tyr Arg Ile Ser Gly Ser Phe Asn Tyr Leu Met His Thr
 1775 1780 1785

 gta ttt aca gat atg aac gat tac tat agt ttt tat gag aaa ata ata 7638
 Val Phe Thr Asp Met Asn Asp Tyr Tyr Ser Phe Tyr Glu Lys Ile Ile
 1790 1795 1800

 tta act aat tct tca att agt gga tct gca tgc agc ttt gtt ctt gag 7686
 Leu Thr Asn Ser Ser Ile Ser Gly Ser Ala Ser Ser Phe Val Leu Glu
 1805 1810 1815 1820

 caa ata aag gaa aca aac gaa ctg tca gtg tga aagtgtgatg tgtacttact 7739
 Gln Ile Lys Glu Thr Asn Glu Leu Ser Val
 1825 1830

[illegible]

Gly Ser Ser Leu Pro Ser Thr Met Lys Leu Asp Phe Met Pro Gly Lys
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Gly Leu Val His Lys Ser Leu Gln Thr Arg Leu Tyr Ser Asn Asp Gln
85 90 95

Thr Lys Ser Val Asn Val Lys Leu Leu Asn Ala Pro Gln Leu Ile Asn
100 105 110

Val Leu Asp Pro Thr Lys Thr Ile Asp Met Glu Val Thr Leu Gly Gly
115 120 125

Arg Ser Leu Thr Thr Thr Asn Ser Val Leu Glu Ala Lys Thr Leu Phe
130 135 140

Pro	Asp	Gly	Lys	Thr	Gly	Asp	Ala	Ser	Ala	Leu	Leu	Asn	Leu	Asp	Ile
145					150					155					160

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Ser Gly Leu Val Ser Leu Val Ile Ser Gln Ala Val Thr Ala Gly
180 185 190

<210> 9

<211> 889

<212> PRT

<213> Salmonella typhi

<400> 9

Met Tyr Tyr Leu Leu Gly Leu Cys Ser Phe Thr Ser Gln Ala Thr Leu
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Ile Pro Pro Pro Gly Phe Glu Ser Leu Leu Glu Gly Gln Thr Glu Gln
20 25 30

Ile Glu Val Leu Leu Pro Gly His Ser Leu Gly Leu Phe Pro Val Val
35 40 45

Val Lys Pro Asp Thr Val Gln Phe Met Ser Pro Leu Met Val Leu Glu
50 55 60

Ser Ser Gly Leu Ala Ala Leu Pro Ala Ala Glu Arg Gln Lys Ala Leu
65 70 75 80

Ala Ala Leu Ser Arg Pro Leu Leu Arg Asn Ser Asn Leu Val Cys Gly
85 90 95

Val Ser Glu Ala Lys Asp Ser Ser Glu Cys Gly Tyr Val Ala Thr Asp
100 105 110

Lys Glu Asp Val Ala Val Ile Phe Asp Glu Asn Asn Ala Gln Leu Ser
115 120 125

Leu Phe Leu Asn Arg Asp Trp Leu Pro Asp Glu Glu Arg Arg Asp Lys
 130 135 140
 Arg Trp Leu Thr Pro Thr Pro Glu Gly Val Ser Ala Phe Ile His Arg
 145 150 155 160
 Gln Thr Leu Tyr Leu Ser Asp Asp Leu His Ser Arg Asn Met Thr Leu
 165 170 175
 Asn Gly Ser Gly Ala Leu Gly Leu Gly Asp Gly Arg Tyr Leu Gly Gly
 180 185 190
 Asp Trp Ala Ala Ile Trp Asn Gln Ser Glu His Tyr Asn Asn Ser Gln
 195 200 205
 Ala Trp Phe Asp Asn Leu Phe Val Arg Gln Asp Leu Gly Asn Gln Tyr
 210 215 220
 Tyr Leu Gln Ala Gly Arg Met Asp Gln Arg Asn Leu Ser Ser Ala Thr
 225 230 235 240
 Gly Gly Asp Phe Gly Phe Ser Leu Leu Pro Leu Ser Arg Phe Asp Gly
 245 250 255
 Leu Arg Thr Gly Thr Thr Gln Ala Tyr Val Asn His Glu Val Asp His
 260 265 270
 Asn Ala Thr Pro Val Met Val Gln Val Thr Arg Asn Ala Arg Ile Asp
 275 280 285
 Ile Tyr Arg Gly Ser Glu Leu Leu Gly Ser Gln Phe Leu Thr Pro Gly
 290 295 300
 Met His Thr Leu Asp Thr His Ser Leu Pro Pro Gly Ser Tyr Pro Leu
 305 310 315 320
 Ala Leu Arg Val Tyr Glu Asp Gly Ile Leu Arg Arg Thr Glu Thr Gln
 325 330 335
 Pro Phe Ser Lys Gly Gly Asn Ser Phe Ser Ala Gln Thr Gln Trp Phe
 340 345 350
 Ile Gln Gly Gly Leu Glu Asp Thr Gly Asp Lys Ala Ser His Tyr Asp
 355 360 365
 Gly Glu Thr Val Met Ala Ala Gly Phe Gln Thr Gly Leu Arg Lys Asn
 370 375 380
 Ile Ser Leu Thr Glu Gly Ile Ser Leu Ala His Glu Ala Trp Tyr Ser
 385 390 395 400
 Glu Thr Arg Leu Asn Ser Gln His Ala Val Leu Asp Gly Thr Leu Asp
 405 410 415
 Leu Ser Ala Gly Ile Leu His Gly Thr Asp Ser Thr Ser Gly Asn Thr
 420 425 430
 Glu Gln Val Thr Tyr Asn Asp Gly Phe Ser Ala Ser Leu Trp Arg Asn
 435 440 445

His Thr Glu Ser Asp Ala Cys Ser Gly Arg His Pro Gln Ser Val His
450 455 460

Ala Ser Met Thr Cys Gln Thr Ser Met Asn Ala Ser Leu Ser Val Ser
465 470 475 480

Val Gly Asn Trp Tyr Ala Leu Leu Gly Tyr Ser Thr Ser Arg Thr Glu
485 490 495

Gly Arg Pro Val Tyr Arg Gly Tyr Asp Asp Asn Ser Asp Lys Glu Asn
500 505 510

Val Phe Trp Arg Gln Ala Tyr Ile Pro Ala Ser His Arg Glu Ser Ala
515 520 525

Gln Ala Ser Ala Thr Tyr Ser Leu Asn Met Ala Gly Met Asn Ile Asn
530 535 540

Thr His Gly Gly Val Trp Arg Thr Arg Asn Asp Gly Val Asn Asp Asp
545 550 555 560

Gly Leu Phe Met Ser Val Ser Val Ser Tyr Ala Ser Gln Pro Pro Thr
565 570 575

Met Thr Gly Ser Asn Arg Tyr Thr Ser Ala Gly Thr Asp Ile His Ser
580 585 590

Ser Arg Asn Gln Lys Thr Gln Thr Ser Trp Asn Val Asn His Val Arg
595 600 605

Ser Trp Gln Gln Asp Leu Tyr Arg Glu Leu Ser Val Gly Phe Ser Gly
610 615 620

Tyr Asn Asp Asp Ser Trp Ser Gly Ser Leu Gly Gly Arg Met Ser Gly
625 630 635 640

Arg Met Gly Glu Leu Ser Ala Thr Ile Ser Asn Ser His Gln Arg Asn
645 650 655

Ala Gly Ser Ala Ser Ser Leu Thr Ala Gly Tyr Ser Ser Ser Leu Ala
660 665 670

Leu Ser Arg Asn Gly Leu Phe Trp Gly Gly Gly Gln Asp Gly Glu Pro
675 680 685

Ala Ser Gly Met Ala Val Asn Val Glu Ser Glu Gly Asp Glu Gly Ser
690 695 700

Ser Gly Lys Val Val Ser Val Arg Gly Ser Ser Gln Pro Phe Ser Leu
705 710 715 720

Gly Phe Gly Gln Gln Ser Leu Leu Leu Met Glu Gly Tyr Asn Ala Thr
725 730 735

Glu Val Thr Ile Glu Asp Ala Gly Val Ser Ser Gln Gly Met Ala Gly
740 745 750

Val Lys Ala Gly Gly Gly Ser Arg Cys Tyr Phe Leu Thr Pro Gly His
755 760 765

[illegible]

Leu Ala Lys Ile Pro Thr Ser Gly Thr Trp Lys Ala Thr Leu Val Leu
165 170 175

Asp Ile Thr Leu Asn Val Thr Asp His Phe Ala Glu Asn Ala Ala Ile
195 200 205

His Arg Met Asn Ala Ser Gln Met Ser Gly Arg Ala Asn Leu Asp Met
225 230 235 240

Glu Gly Ser Asn_Lys Ser_Gly Thr Gly_Phe_Gln Val_Ile Lys Ser_Asp
 260 265 270

Ser Ile Pro Val Thr Arg Gly Val Glu Phe Ser Leu Asp Asn Val Asp
290 295 300

Arg Cys Val Pro Val Pro Leu Thr Leu Thr Thr Gln Pro Phe Asn Ile
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Leu Met Gly Thr Gln Thr Pro
355

<400> 11
Met Thr Val Tyr Leu Asp Asp Lys Asp Lys Glu Leu Leu Lys Glu Ile
1 5 10 15

Leu Thr Pro Thr Pro Cys Phe Lys Arg Leu Lys Lys Leu Lys Asp Arg
35 40 45

Gly Val Ile Ile Gly Gln Phe Ala Leu Leu Asp Lys Glu Lys Leu Gly
50 55 60

[illegible]

Date of Deposit: 26 November 2001

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:

FOLKESSON et al.

Serial No.: PCT/SE00/01079

Art Unit: (unassigned)

Filing Date: Herewith

Examiner: (unassigned)

Title: FIMBRIAL PROTEINS

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to calculating the filing fee and examination of the above-identified application on the merits, please enter the following amendments.

AMENDMENT

In the Claims:

Please amend claims 10 and 11 as follows.

10. (Amended) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 4 to said mammal.

11. (Amended) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 5 to said mammal.

Please add the following new claims.

15. (New) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 6 to said mammal.

16. (New) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 8 to said mammal.

17. (New) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 7 to said mammal.

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PATENT

18. (New) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 9 to said mammal.

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

Claims 10 and 11 have been amended as follows.

10. (Amended) A method for [protection] vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to [any of claims] claim 4[, 6, and 8] to said mammal.

11. (Amended) A method for [protection] vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to [any of claims] claim 5[, 7, and 9] to said mammal.

New claims 15-18 have been added.

--15. (New) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 6 to said mammal.

16. (New) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to claim 8 to said mammal.

17. (New) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 7 to said mammal.

Atty Dkt No. ABR 022 US
35 U.S.C. §371 of PCT/SE00/01079
PATENT

18. (New) A method for vaccinating a mammal against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to claim 9 to said mammal.--

Atty Dkt No. ABR 022 US
35 U.S.C. §371 of PCT/SE00/01079
PATENT

REMARKS

Introductory Comments:

The present application is a 35 U.S.C. §371 filing of International Application Number PCT/SE00/01079, filed 26 May 2000.

Overview of the Amendments:

Applicants, by way of this preliminary amendment, have entered minor claim amendments and four new claims for consideration herein. Applicants respectfully request that these amendments be entered prior to calculation of the filing fees, and prior to examination of the present application on the merits.

More particularly, applicants have amended claims 10 and 11 merely to remove multiple dependencies and to recite the invention with greater particularity. Support for these claim amendments can be found in the claims as originally filed and throughout the specification, for example, at page 6, line 15 through page 7, line 11. In addition, applicants have submitted herewith new claims 15-18. Support for these new claims can be found throughout the specification and claims, particularly in claims 10 and 11 as originally filed and in the specification at page 6, line 15 through page 7, line 11. Accordingly, applicants submit that no new matter has been added by way of the above-described claim amendments and the new claims, and the entry thereof is respectfully requested.

The claim amendments and the new claims have been provided in both “clean version” and in “marked-up version” in conformance with 37 C.F.R. §1.121(c). The “marked-up version” of these amendments and new claims shows the changes made to the claims by the current amendment. The attached pages are captioned “VERSION WITH MARKINGS TO SHOW CHANGES MADE”.

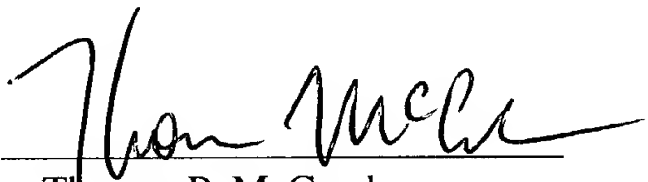
Atty Dkt No. ABR 022 US
35 U.S.C. §371 of PCT/SE00/01079
PATENT

CONCLUSION

Applicants respectfully submit that the claims define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect would be appreciated.

Respectfully submitted,
SBL Vaccin AB

Date: 22 November 2001

By: 
Thomas P. McCracken
Registration No. 38,548

POWDERJECT TECHNOLOGIES, INC.
6511 Dumbarton Circle
Fremont, CA 94555
Telephone: (510) 742-9700, ext. 209
Fax: (510) 742-9720

FIMBRIAL PROTEINSField of the invention

The present invention is based on the finding that two fimbrial operons, the *saf* operon and the *tcf* operon, are specific for *Salmonella enterica* subspecies 1 bacteria and therefore have therapeutic use. Due to their specificity they can be used to provide vaccines against *Salmonella enterica* subspecies I as well as for detection of *Salmonella enterica* subspecies I. The *saf* operon is specific for all *Salmonella enterica* subspecies 1 bacteria and the *tcf* operon is specific for the serovar Typhi of *Salmonella enterica* subspecies 1.

- 10 All or part of the DNA-sequences of the genes encoding these proteins can be used as active agents in a vaccine against diseases caused by the *Salmonella enterica* subspecies I bacterial strains or for detection of said bacterial strains.

The present invention also relates to methods of isolating these fimbrial proteins, to antibodies directed against these proteins, and to a vaccine composition comprising these proteins or antibodies directed against these proteins for use in the treatment of infections caused by the *Salmonella spp.* The fimbrial proteins according to the invention or antibodies directed against them can be used for detection of *Salmonella spp.* bacteria.

20

Background of the invention

The members of genus *Salmonella spp* colonize and infect a wide range of different organisms. Many cause gastroenteritis and enteric fever in humans and domesticated animals while others are not associated with human disease (Saylers et al, 1994). The genus has been divided into two species, *Salmonella bongori* and *Salmonella enterica* where *enterica* can be further subdivided into seven subspecies, designated I, II, IIIa, IIIb, IV, VI, and VII (Reeves et al, 1989). *Salmonella enterica* subspecies I are preferentially associated with warm-blooded animals. Over 99% of all clinical *Salmonella* isolates are strains belonging to this subspecies, including serovars Typhimurium and Enteritidis, which are the major causes of *Salmonella* induced gastroenteritis in humans, and Typhi, the human specific causative organism of typhoid fever, the most severe form of human salmonellosis (Popoff et al, 1992).

- 35 *Salmonella enterica* subspecies I consists of over 1300 different serovars and is preferentially associated with warm-blooded animals (Bäumler, 1997). Over 99% of all clinical *Salmonella* isolates are strains belonging to this subspecies,

including serovars Typhimurium and Enteritidis, which are the major causes of *Salmonella* induced gastroenteritis in humans, and Typhi, the human specific causative organism of typhoid fever, the most severe form of human salmonellosis (Popoff and Le Minor, 1992).

5

Today gastroenteritis and enteric fever can neither be prevented nor treated with good results. Typhoid fever is a substantial public health problem in developing countries. Each year 33 million people become ill and over 500 000 people die from this infection (American Institute of Medicine, 1986). Typhoid fever can be prevented by vaccination with attenuated bacteria, such as Ty21 and Vi vaccines and whole cell vaccines. Whole cell vaccines show a high incidence of side effects (Ashcroft et al, 1964, Yugoslav Typhoid commission, 1964). The vaccines consisting of attenuated strains of *Salmonella typhi* suffer from serious drawbacks. They must be administered as three or four spaced doses in order to stimulate protective immune responses (Levine et al, 1989). The treatment of *Salmonella typhi* with antibiotics is jeopardized since there are strains of *Salmonella typhi* that are resistant to chloramphenicol, ampicillin, and trimethoprim as well as ciprofloxacin (i.e. multidrug-resistant strains) (Rowe et al, 1997).

20

Accurate detection of *Salmonella enterica* subspecies I is today not possible. *Salmonella enterica* subspecies I can today only be detected by antibodies directed against surface proteins of *Salmonella enterica* subspecies I. The use of the sequences according to the invention makes it for the first time possible to rapidly and accurately determine the presence of *Salmonella enterica* subspecies I.

25

For many pathogenic bacteria, there is evidence that the filamentous surface protein structures called pili (fimbriae) are connected to the adhesion of the bacteria to the host cells. Pili proteins are very antigenic and are easily purified. Therefore pili preparations have been used as antigens for vaccination.

30

Summary of the invention

35

The invention relates to the objects as defined in the claims. The main object of the present invention is to provide two fimbrial proteins that are specific for *Salmonella enterica* subspecies I bacterial strains, the nucleotide sequences

encoding said proteins, as well as the corresponding amino acid sequences of for therapeutic and diagnostic use. Further are recombinant microorganisms provided, in which the nucleotide sequences according to the invention have been inserted.

5 An object of the present invention is to provide vaccine compositions for use in the treatment of *Salmonella enterica* infective strains, essentially pure Saf and Tcf fili protein of *Salmonella enterica* subspecies I and *Salmonella enterica* subspecies I serovar Typhi, respectively, as well as antibodies directed to these
10 fili proteins.

A further object of the present invention is to provide the DNA sequences of the genes encoding the Saf and Tcf proteins. These sequences can be used for recombinant production of the proteins and for the preparations of vector
15 vaccines against *Salmonella enterica* subspecies 1 and *Salmonella enterica* subspecies 1 serovar Typhi, respectively, as well as for diagnostic purposes.

Yet another object of the present invention to use purified Saf and Tcf protein from *Salmonella enterica* subspecies 1 bacteria for active or passive
20 immunization of mammals, i.e. the proteins according to the invention can be comprised in a vaccine composition or be used to raise antibodies which can be comprised in a vaccine composition.

Finally, an object of the present invention is to provide a method for preventing
25 or reducing the possibility of *Salmonella* infection of a mammal by administering the vaccines according to the invention. The invention may be more fully understood by reference to the following drawings and detailed description.

30 Brief description of the drawings

Figure 1.

Schematic representation of phage clones (named N10, D1, B1, F11) covering the entire cs7 insert of *Salmonella enterica* serovar Typhimurium strain SR χ 3181, i.e. comprising the *saf* fimbrial operon, i.e. *safA*, *B*, *C* and *D*
35 (SEQ ID NO 1).

The clones were selected from partial *Eco* RI and *Bam*HI libraries in the Lambda Dash II vector. The cs7 insert is represented by a bold line. The extent

Figure 2: Schematic representation of the pTY52 cosmid comprising the *tcf*-operon (SEQ ID NO 2).

Figure 3: The phylogenetic distribution of the identified genes on the cs7 insert was investigated using the well defined SARC collection, see Example 1.

15 Sequence listing

Sequence Listing No. 2, herein referred to as SEQ ID NO 2, —DNA sequence of
20 the genes which encode the precursor of the tcf fimbrie unit of *Salmonella*
enterica subspecies I serovar Typhi.

The phages carrying the inserted SEQ ID NO 1, i.e. phages clones B1, D1, F11
25 and N10 (see Figure 1) have been given the ECACC Accession numbers
99051922, 99051923, 99051924, and 99051925, respectively.

The depositions were made May 19, 1999.

The present invention is based on the finding that two fimbrial operons, the *saf* operon and the *tcf* operon, are specific for *Salmonella enterica* subspecies 1 bacteria. Due to their specificity they can be used to provide vaccines against *Salmonella enterica* subspecies I as well as detection methods for *Salmonella enterica* subspecies I. The *saf* operon is specific for all *Salmonella enterica*

subspecies 1 bacteria and the *tcf* operon is specific for the serovar typhi of *Salmonella enterica* subspecies 1, see Examples 1 & 2.

The main object of the invention relates to two fimbrial operons, the *saf* operon
5 and the *tcf* operon, that are specific for *Salmonella enterica* subspecies 1 bacteria for therapeutic use.

Another object of the present invention is to provide vaccines against *Salmonella enterica* subspecies 1 induced gastroenteritis, enteric fever and
10 typhoid fever.

A further object of the present invention is to provide methods to detect *Salmonella enterica* subspecies 1. The nucleotide sequences according to the invention are useful for constructing vectors for use as vaccines for insertion
15 into attenuated bacteria in constructing a recombinant vaccine, for insertion into a viral vector in constructing a recombinant viral vaccine, or for direct inoculation as a nucleic acid vaccine. The pili proteins according to the invention, or antigenic fragments thereof, can be used for active immunization and antibodies directed against them can be used for passive immunization. All
20 these applications of the sequences according to the invention are obtained by applying standard techniques known to the man ordinary skilled in the art.

Vaccines against *Salmonella enterica* subspecies I.

The genes encoding the *saf* and *tcf* fimbrial structures, or fragments thereof,
25 may be incorporated into a bacterial or viral vaccine comprising recombinant bacteria, virus or fungi which are engineered to produce one or more immunogenic epitopes of the *saf* or *tcf* fimbrial structures. In addition, the genes encoding the *saf* and *tcf* fimbrial structures, or part thereof, operatively linked to regulatory elements, can be introduced directly as a nucleic acid
30 vaccine, to elicit a protective immune response.

The proteins or antigenic fragment thereof, deduced from the nucleic acid sequences of the present invention are useful alone or in conventional vaccine mixtures in the vaccine compositions according to the invention. The proteins
35 could be produced by chemical synthesis or recombinant expression according to conventional methods.

The proteins and peptides according to the invention can be obtained by using a host organism transformed or transfected with an expression vector obtained by insertion of a gene according to the invention, or part thereof, into a vector in a conventional manner. The vector which is used to construct the expression
5 vector is not particularly limited, but specific examples include plasmids such as pET (Stratagen) and the like; and phages such as M13 (NEB), phage display libraries and the like. As expression regulatory sequence can among others T7 promoters and lac promoters be used.

10 An appropriate host to be transformed or transfected with the expression vector can be chosen among for example *E.-coli*, *Salmonella* or *Bacillus subtilus*. The transformed or transfected host is cultured and proliferated under suitable conditions.

15 After culturing, the peptides of the present invention may be purified by, for example, chromatography, precipitation, and/or density gradient centrifugation. The thus obtained peptides can be used as a vaccine or for the production of antibodies directed against said peptides, which can be used for passive immunization.

20

The purified preparation containing one or several proteins according to the invention, or parts thereof, is then formulated as a pharmaceutical composition, as for example a vaccine, or in a mixture with adjuvants. If
25 desired the proteins are fragmented by standard chemical or enzymatic techniques to produce antigenic segments.

In formulating the vaccine compositions with the peptide or protein, alone or in various combinations, the immunogen is adjusted to an appropriate concentration and formulated with any suitable vaccine adjuvant. The
30 immunogen may also be incorporated into liposomes, or conjugated to polysaccharides and/or other polymers for use in a vaccine formulation.

The different vaccines according to the present invention are administered to mammals in many different ways. These include intradermal, intramuscular,
35 intraperitoneal, intravenous, subcutaneous, oral, and intranasal routes of administration. The vaccine doses will differ depending on circumstances such

as body weight, interferences with other administered medicaments etc. The upper limit is not critical unless the dose shows toxicity.

The peptides and proteins of the present invention are also useful to produce
 5 monoclonal or polyclonal antibodies for use in passive immunotherapy against *Salmonella enterica* subspecies 1. Human immunoglobulin is preferred. Antisera is obtained from individuals immunized with proteins or peptides according to the invention. The immunoglobulin fraction is then enriched, for example by immunoaffinity or affinity chromatography. Antibodies raised in
 10 a suitable mammal or in the patient to be treated, can subsequently be administered locally or topically, e.g. orally to the patient.

Detection of *Salmonella enterica* subspecies I in general.

The sequences according to the invention, or part thereof, or fragments
 15 hybridizing therewith, as well as the proteins according to the invention, or part thereof, and antibodies directed to said proteins, or antigenic fragments thereof, can be used in molecular diagnostic assays for the detection of *Salmonella enterica* subspecies I.

20 Nucleic acids having the nucleotide sequence according to the invention, or any nucleotide sequence hybridizing therewith can be used as a probe in nucleic acid hybridization assays for the detection of *Salmonella spp* in various tissues and body fluids of patients. The hybridization assay may be of any type including; Southern blots, Northern blots, colony blots.

25 PCR technology is the most preferred technology for detection according to the invention of *Salmonella enterica* subspecies 1. Primers of at least one selected from the 5' end and one from the 3' end can be used in PCR and other known tests to rapidly identify the presence of *Salmonella enterica* subspecies 1. This is
 30 according to conventional techniques.

The isolated and purified proteins and peptides of the invention can be used as diagnostics to measure an increase in serum titer of *Salmonella enterica*
 subspecies I-specific antibody since they bind strongly to these antibodies. A
 35 serum test sample can be screened for *Salmonella enterica* subspecies I by methods such as for example ELISA.

The invention further comprises the use of antibodies directed against the *saf* and *tcf* fimbriae structures for quantitative or qualitative determinations of the pili proteins of the invention, or fractions thereof, in cells, tissues or body fluids.

5

Detection of *Salmonella enterica* subspecies I by using nucleic acid hybridization technology

10

Nucleic acid hybridization technology can also be used to detect *Salmonella enterica* subspecies I according to the invention. The nucleic acid probes chosen from parts of the sequences according to the invention can be either DNA or RNA. DNA sequences complementary to the sequences according to the invention can also be used. The binding of the probe to the target sequence, i.e. the hybridization, must not be perfect. Variations and mutations of the sequences according to the invention can be used as long as they hybridize good enough to detect *Salmonella enterica* subspecies I. The preferred length of the nucleic acid probes is about 10 to 400 nucleotides, most preferred not longer than 100 nucleotides.

20

The nucleotide probe is preferably chosen from the parts of the sequences that have the least variation. In the most preferred embodiments when screening for SEQ ID NO 1 (the *saf* operon, specific for *Salmonella enterica* subspecies I) a nucleotide probe or PCR primer selected from nucleotides 37 368-37 868 should be avoided since this region is hypervariable.

25

The nucleic acid probes according to the invention are prepared by any conventional method such as organic synthesis, recombinant techniques, or isolation from genomic DNA.

30

The nucleic acid probes of the invention are labeled in a conventional manner to signal hybridization to target nucleic acid from *Salmonella enterica* subspecies I. The labeling may comprise a radiolabel, an enzyme, a bacterial label, a fluorescent label, an antibody, an antigen, a latex particle, an electron dense compound, or a light scattering particle.

35

The probes may be provided in a lyophilized form, to be reconstituted in a buffer appropriate for hybridization, or the probes may already be present in

such a buffer. The buffer may contain a suitable hybridization enhancer, detergent, carrier DNA, and a compound to increase the specificity.

Any conventional hybridization assay technique, such as dot blot hybridization, Southern blotting, sandwich hybridization, displacement hybridization and the like, can be used.

The target analyte polynucleotide of a microorganism may be in various media, most often in a biological, or physiological specimen. In most cases it is preferred to subject the specimen containing the target polynucleotide to any conventional extraction, purification, and/or isolation before conducting the analysis.

The sample containing the target analyte nucleotide sequence must often be treated to convert the DNA to a single-stranded form, which may be accomplished by a variety of conventional techniques, such as thermal or chemical techniques.

The following examples describe the isolation and specificity of the sequences according to the invention.

EXAMPLE 1

Identification and characterization of the *saf* operon.

The present inventors found, upon investigation of a 7 kb chromosomal region on centisome 7 originally isolated from the *S. typhimurium* strain SR-11 k3181, a region that exhibits many of the traits that define a pathogenicity island. It has a lower G+C composition than the average composition of the *Salmonella* genome and includes many sequences related to different mobile genetic elements. The region is not present in *E.coli* K12, and the *Salmonella* specific DNA is inserted between the tRNA gene *aspV* and the stop codon of *yafV*, a hypothetical protein upstream of the *yafH* gene at 5 min in the *E.coli* chromosome. This *Salmonella* specific insert encodes proteins creating adhesive structures and other virulence factors. Sequencing revealed genes encoding a new fimbrial operon that they designated *Salmonella* Atypical Fimbriae (*saf*), due to its relatedness to a subgroup of adhesive structures forming thin atypical fimbriae or non-fimbrial adhesins.

The *saf* operon consists of four contiguous genes, *safA*, *safB*, *safC* and *safD* that encode fimbrial subunit, periplasmic chaperone, outer membrane usher protein and alternative fimbrial subunit, respectively. The genes *safA*, *B*, *C* and *safD* encode putative proteins of 166, 244, 836 and 156 amino acids, respectively. Analyzes of clinical *Salmonella* isolates showed that DNA of 195 out of 198 clinical isolates belonging to *S. enterica* subspecies I hybridized with *safB* and *safC*, i.e. these sequences are common to more than 99% of the known *Salmonella enterica* subspecies I bacteria. The inventors showed that 58% of these clinical isolates carry the *safA*, see Table 1.

Table 1. The prevalence of the *saf* genes in clinical *Salmonella* isolates.

Serovar	<i>safA</i>	<i>safB</i>	<i>safC</i>	# isolates
<i>S. adelaide</i>	-	+	+	1
<i>S. agona</i>	+	+	+	6
<i>S. anatum</i>	-	+	+	3
<i>S. bareilly</i>	+	+	+	3
<i>S. blockley</i>	+	+	+	3
<i>S. bovismorbificans</i>	-	+	+	5
<i>S. braenderup</i>	-	+	+	4
<i>S. brandenburg</i>	+	+	+	1
<i>S. bredeney</i>	+/-	+	+	15
<i>S. chester</i>	+	+	+	1
<i>S. colindale</i>	-	+	+	1
<i>S. derby</i>	-	+	+	1
<i>S. dublin</i>	-	+	+	1
<i>S. eastbourne</i>	+	+	+	2
<i>S. emek</i>	+	+	+	1
<i>S. enteritidis</i>	-	+	+	8
<i>S. give</i>	-	+	+	1
<i>S. goettingen</i>	+	+	+	1
<i>S. haardt</i>	-	+	+	1
<i>S. hadar</i>	+	+	+	16
<i>S. heidelberg</i>	-	+	+	1
<i>S. hittingfoss</i>	+	+	+	5
<i>S. infantis</i>	-/+	+	+	6
<i>S. java</i>	-	+	+	1
<i>S. javiana</i>	-	+	+	1
<i>S. kottbus</i>	-	+	+	1
<i>S. livingstone</i>	-	+	+	1
<i>S. london</i>	+	+	+	1
<i>S. maastricht</i>	+	+	+	2
<i>S. mbandaka</i>	-	-	-	3
<i>S. montevideo</i>	+	+	+	1
<i>S. muenster</i>	-	+	+	1
<i>S. newport</i>	+	+	+	2
<i>S. ohio</i>	+	+	+	1
<i>S. oranienburg</i>	+	+	+	2
<i>S. panama</i>	+	+	+	3
<i>S. potsdam</i>	+	+	+	1
<i>S. rissen</i>	-	-	-	1
<i>S. saarbrücken</i>	-	+	+	1
<i>S. saint paul</i>	+	+	+	3
<i>S. schwartzengrund</i>	-	+	+	1
<i>S. singapore</i>	+	+	+	1
<i>S. stanley</i>	+	+	+	5
<i>S. subsp I 4.5,12:-:-</i>	+	+	+	2
<i>S. subsp I 4.5,12:b:-</i>	-	+	+	1
<i>S. subsp I 4.5,12:i:-</i>	+	+	+	1
<i>S. subsp I spont</i>	-	+	+	1
<i>S. tennessee</i>	+	+	+	2
<i>S. thompson</i>	-	+	+	1
<i>S. typhi</i>	-	+	+	1
<i>S. typhimurium</i>	+	+	+	27
<i>S. virchow</i>	+	+	+	7
<i>S. weltevreden</i>	-	+	+	1
<i>S. worthington</i>	-	-	-	2
<i>S. subsp III</i>	-	-	-	1

The phylogenetic distribution of the identified genes on the cs7 insert was investigated using the well defined SARC collection, which showed that the presence of the *safA*, *safB*, *safC* and *safD* genes is restricted to *S. enterica* subspecies I (Fig. 3). This region is hence the first subspecies I specific genetic region to be identified with a broad distribution within the subspecies. Since the serovars of subspecies I constitute over 99% of human salmonellosis and are preferentially associated with warm blooded animals, it implicates a role for the *saf* adhesive organelle in the colonization of these organisms.

EXAMPLE 2

Identification and characterization of the *tcf* operon.

The present inventors found that *Salmonella enterica* subspecies I serovar Typhi contains DNA encoding an additional fimbrial operon, the *tcf* operon, in the *sinR-pagN* intergenic region. Southern blot analysis revealed a markedly different restriction pattern in *S. enterica* serovar Typhi than the other subspecies I isolates, suggesting that the *saf-sin* region in serovar Typhi might carry additional DNA relative to serovar Typhimurium strains. A PCR reaction (using a kit from Roche) was therefore performed using a *sinR* (5'-GTA AAT CGC TTA GTC GCC-3') specific forward primer and a *pagN* (5'-TCA ACT CAA CCT TCA GCC-3') specific reverse primer.

This primer pair produced, as expected, a product of 2 kb in serovar Typhimurium from the SARC collection, while from serovar Typhi the product was 10 kb. Thus, the neighboring *sinR* and *pagN* genes in serovar Typhimurium strains are separated by approximately 8 kb in serovar Typhi.

The Typhi specific PCR product was purified, digested partially with *EcoRI* and sub-cloned into pUC18 forming a set of overlapping clones. Sequencing of the clones revealed a putative fimbrial operon designated *tcf* for Typhi Colonizing Factor. Four ORFs, *tcfA,B,C,D*, have been identified with putative proteins having significant homology to CooB (38% identical over 192 aa), CooA (37% identical over 170 aa), CooC (34% identical over 872 aa) and CooD (31% identical over 272 aa), respectively. The Coo proteins are involved in the biosynthesis of the CS1 colonizing factor antigens of enterotoxigenic *E.coli* (Fig. 4) (Froehlich et al., 1994). The peptide of the *tcfB* ORF is also homologous to the CblA major fimbrial subunit protein (45% identical over 154 aa) of the cable

type II pili of the cystic fibrosis-associated *Burkholderia cepacia* (Sajjan et al., 1995). Down-stream of the *tcf*-operon two ORFs were identified with the same transcriptional orientation as the *tcf* genes. The first was designated *tinR* for Typhi insert regulator because it is homologous (33% identical over 144 aa) to AzlB of *Bacillus subtilis*, a member of the Lrp/AsnC family of transcriptional regulators (Belitsky et al., 1997). *tinR* is followed by an ORF (*tioA* for Typhi insert orf) encoding a putative protein of 205 amino acids with no significant homologies to anything in the DDBJ/EMBL/GenBank databases. The above sequence from *Salmonella enterica* serovar Typhi strain RKS 3333 and the *tcf* region of the incomplete genome sequence from serovar Typhi strain CT18 ([http:// www.sanger.ac.uk](http://www.sanger.ac.uk)) are 99% identical over the total length of the investigated region in concordance with the clonal nature of the serovar .

A 2 kb large internal *EcoR* I fragment was used as a probe in a Southern blot of the SARC collection. This blot shows that *Salmonella enterica* subspecies I serovar Typhi (SARC2) is the only strain in the collection possessing DNA hybridizing to this fragment (Fig. 4).

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Yugoslav Typhoid Comission. (1964) *Bull. WHO* 30:623-30.

Claims:

1. Peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.
5
2. Antibodies directed against a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.
- 10 3. Nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2) for use in medicine.
4. A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a peptide encoded by a nucleotide sequence selected from
15 Sequence Listing No. 1 (SEQ ID NO 1), or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.
5. A vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a peptide encoded by a nucleotide sequence
20 selected from Sequence Listing No. 2 (SEQ ID NO 2), or antibodies directed against said peptide and, optionally, a pharmaceutically acceptable carrier.
6. A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a nucleic acid sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and, optionally, a pharmaceutically acceptable
25 carrier.
7. A nucleic acid vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2) and, optionally, a pharmaceutically acceptable carrier.
30
8. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I, comprising a host in which a recombinant vector comprising a
35 nucleic acid sequence selected from Sequence Listing No. 1 (SEQ ID NO 1), has been inserted and, optionally, a pharmaceutically acceptable carrier.

9. A vector vaccine for the protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising a host in which a recombinant vector comprising a nucleic acid sequence selected from Sequence Listing No. 2 (SEQ ID NO 2), has been inserted and, optionally, a pharmaceutically acceptable carrier.

5

10. A method for protection against diseases caused by *Salmonella enterica* subspecies I, comprising administering a vaccine according to any of claims 4, 6, and 8.

10 11. A method for protection against diseases caused by *Salmonella enterica* subspecies I serovar Typhi, comprising administering a vaccine according to any of claims 5, 7, and 9.

15 12. Antibodies directed against a peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

20 13. Peptide encoded by a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method.

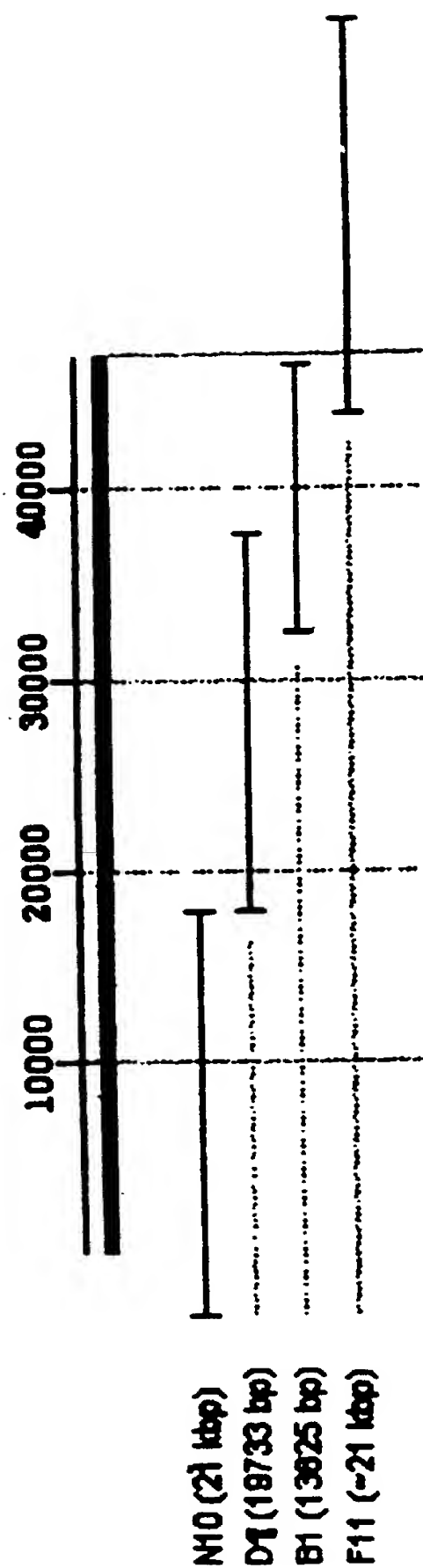
25 14. Primers for, or probes that hybridize with, a nucleotide sequence selected from Sequence Listing No. 1 (SEQ ID NO 1) and Sequence Listing No. 2 (SEQ ID NO 2), for use in a diagnostic method for the purpose of detecting *Salmonella enterica* subspecies I.

ABSTRACT

5 The present invention is based on the finding that two fimbrial structures are specific for *Salmonella enterica* subspecies 1 bacteria. Due to their specificity they can be used to provide vaccines against *Salmonella enterica* subspecies I as well as for detection of *Salmonella enterica* subspecies I.

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Fig. 1



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Fig. 2

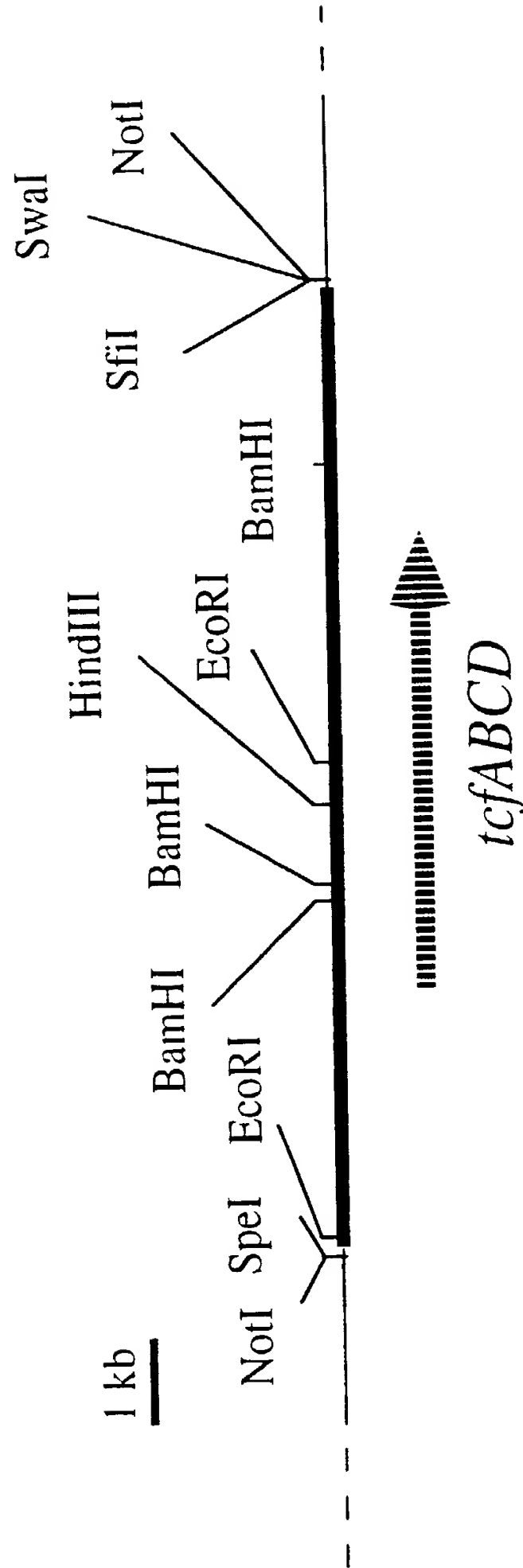
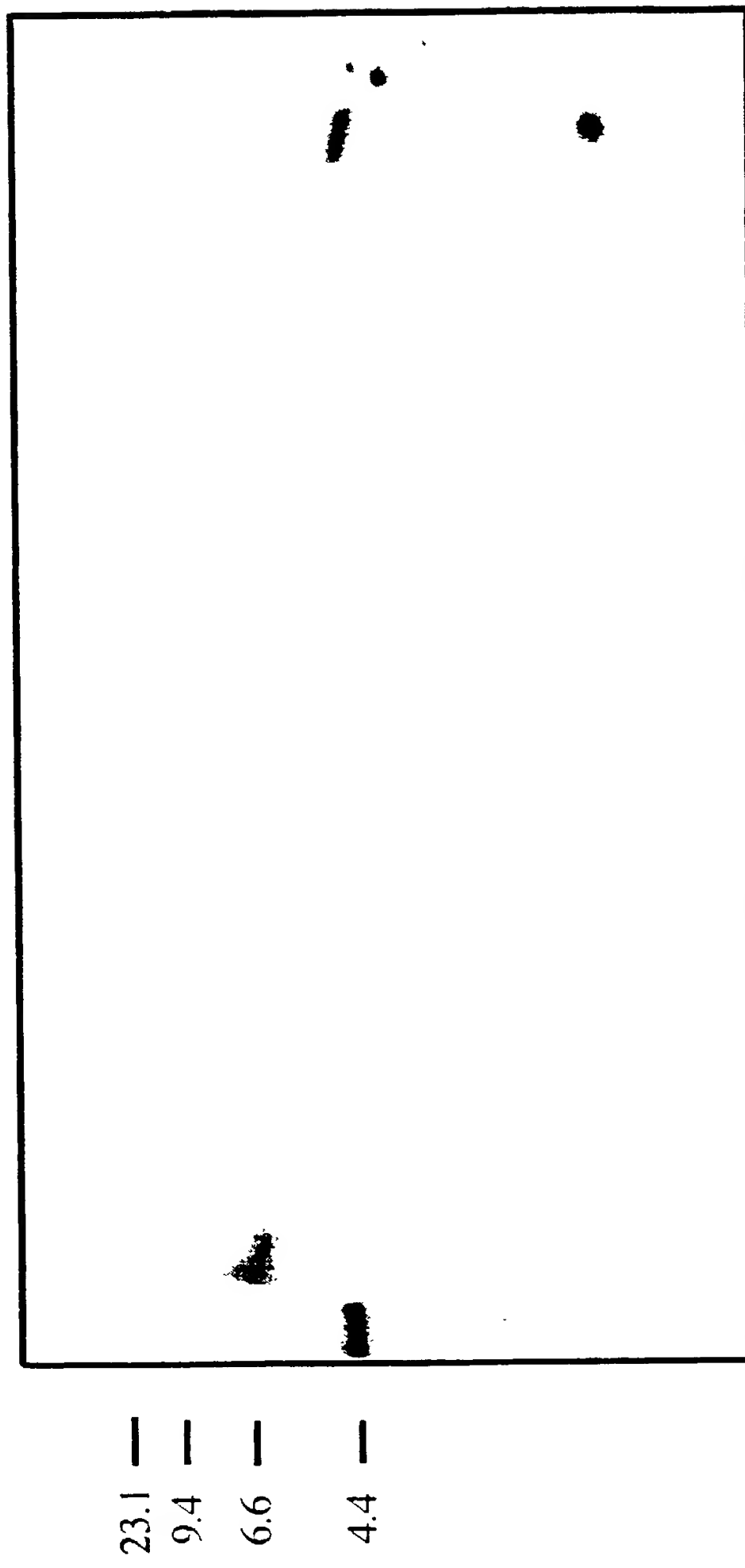
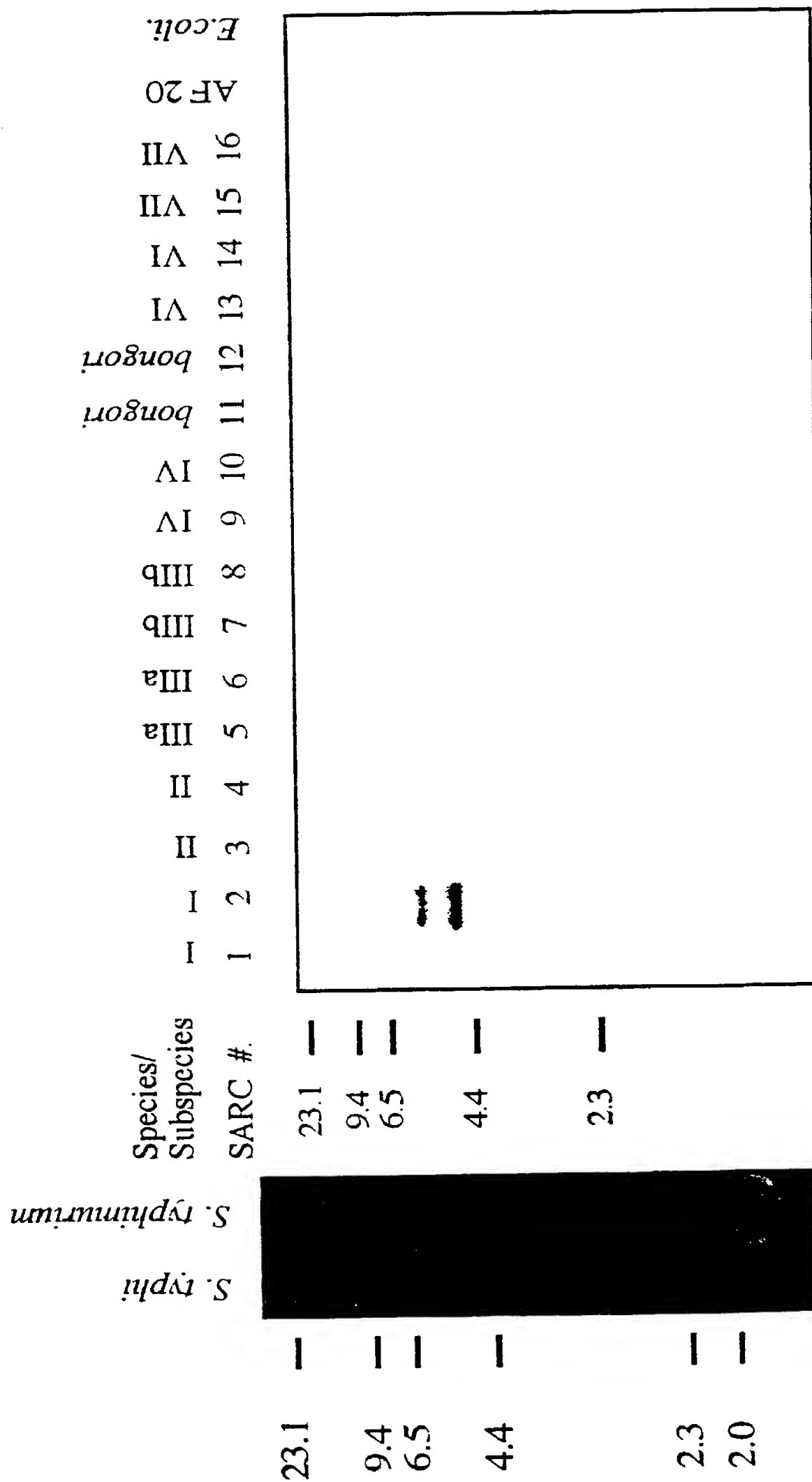


Fig. 3

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23.1 —
9.4 —
6.6 —
4.4 —



Atty Dkt No. ABR 022 US
PATENT



COMBINED DECLARATION AND POWER OF ATTORNEY
FOR UTILITY PATENT APPLICATION

AS A BELOW-NAMED INVENTOR, I HEREBY DECLARE THAT:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if more than one name is listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: FIMBRIAL PROTEINS the specification of which

X was filed on 26 November 2001 and assigned Serial No. 09/926,596; and
X was initially filed in a PCT application designating the US on 26 May 2000, and assigned Serial No. PCT/SE00/01079;

X was amended under PCT Article 19 (35 U.S.C. §371(c)(3)) on 4 September 2001 and on 13 September 2001; and

X has been amended by the Preliminary Amendment dated 22 November 2001.

I HAVE REVIEWED AND UNDERSTAND THE CONTENTS OF THE ABOVE-IDENTIFIED SPECIFICATION, INCLUDING THE CLAIMS, AS AMENDED BY ANY AMENDMENT REFERRED TO ABOVE.

I acknowledge and understand that I am an individual who has a duty to disclose information which is material to the patentability of the claims of this application in accordance with Title 37, Code of Federal Regulations, §§ 1.56(a) and (b) which state:

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(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a *prima facie* case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office,

or

(ii) Asserting an argument of patentability.

A *prima facie* case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

I do not know and do not believe this invention was ever known or used in the United States of America before my or our invention thereof, or patented or described in any printed publication in any country before my or our invention thereof or more than one year prior to said application. This invention was not in public use or on sale in the United States of America more than one year prior to this application. This invention has not been patented or made the subject of an inventor's certificate issued before the date of this application in any country foreign to the United States of America on any application filed by me or my legal representatives or assigns more than six months prior to this application.

I hereby appoint the following attorneys and agents to prosecute that application and to transact all business in the Patent and Trademark Office connected therewith and to file, to prosecute and to transact all business in connection with all patent applications directed to the invention:

3
Thomas P. McCracken, Reg. No. 38,548
Roberta L. Robins, Reg. No. 33,208
Sharon E. Crane, Reg. No. 36,113

Address all correspondence to: Thomas P. McCracken at:
POWDERJECT PHARMACEUTICALS PLC
Florey House
The Oxford Science Park
Oxford OX4 4GA

United Kingdom
Telephone: +44 1865 332 600
Facsimile: +44 1865 332 601

Address all telephone calls to: Thomas P. McCracken in the United Kingdom at +44 1865 332 600.

This appointment, including the right to delegate this appointment, shall also apply to the same extent to any proceedings established by the Patent Cooperation Treaty.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

10

Signature:

Anders Folke

Date 20020702

Full Name of Inventor: Anders FOLKESSON

Citizenship: SE

Residence: Sweden

Post Office Address: Råsundavägen 169B, S-169 36 Solna, Sweden

SEX

20

Signature:

Staffan Norman

Date 20020702

Full Name of Inventor: Staffan NORMARK

Citizenship: SE

Residence: Sweden

Post Office Address: Långängsvägen 27, S-182 75 Stocksund, Sweden

SEX

30

Signature:

Sven Löfdahl

Date 20020702

Full Name of Inventor: Sven LÖFDAHL

Citizenship: SE

Residence: Sweden

Post Office Address: Adolfsbergsvägen 36, S-168 66 Bromma, Sweden

SEX

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tcg	ctc	ttt	aac	cag	ggg	tta	caa	cag	cca	ggg	act	tat	cgc	gtg	gac	38880
Ser	Leu	Phe	Asn	Gln	Gly	Leu	Gln	Gln	Pro	Gly	Thr	Tyr	Arg	Val	Asp	
	455					460					465					
gtg	atg	gtg	aat	ggg	aaa	cgt	gtc	gac	acc	cgt	gat	gtg	gtg	ttc	aaa	38928
Val	Met	Val	Asn	Gly	Lys	Arg	Val	Asp	Thr	Arg	Asp	Val	Val	Phe	Lys	
470					475					480					485	
ttg	gaa	aag	gat	ggg	caa	gga	acg	cct	gtt	ctg	gct	cct	tgt	ttg	acg	38976
Leu	Glu	Lys	Asp	Gly	Gln	Gly	Thr	Pro	Val	Leu	Ala	Pro	Cys	Leu	Thr	
				490				495						500		
gtc	agt	cag	ctt	tca	cgc	tac	ggc	gta	aaa	acg	gaa	gat	tac	cct	cag	39024
Val	Ser	Gln	Leu	Ser	Arg	Tyr	Gly	Val	Lys	Thr	Glu	Asp	Tyr	Pro	Gln	
			505					510					515			
ttg	tgg	aaa	gca	gca	aag	ccc	cca	gat	gag	tgt	gcg	gat	ctg	acc	gcc	39072
Leu	Trp	Lys	Ala	Ala	Lys	Pro	Pro	Asp	Glu	Cys	Ala	Asp	Leu	Thr	Ala	
		520					525					530				
att	cca	cag	gct	aaa	gcg	gta	ctg	gat	atc	aat	aat	cag	caa	ctg	caa	39120
Ile	Pro	Gln	Ala	Lys	Ala	Val	Leu	Asp	Ile	Asn	Asn	Gln	Gln	Leu	Gln	
	535					540					545					
ctg	agt	att	ccg	cag	ttg	gcg	ttg	cgt	ccg	gaa	ttt	aag	ggg	atc	gct	39168
Leu	Ser	Ile	Pro	Gln	Leu	Ala	Leu	Arg	Pro	Glu	Phe	Lys	Gly	Ile	Ala	
550					555					560					565	
cca	gaa	gat	ctt	tgg	gat	gat	ggg	att	ccg	gcg	ttt	ctg	atg	aac	tac	39216
Pro	Glu	Asp	Leu	Trp	Asp	Asp	Gly	Ile	Pro	Ala	Phe	Leu	Met	Asn	Tyr	
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agt	gcg	agg	aca	acg	cag	acg	gat	tac	aaa	atg	gat	atg	gtg	ggg	cgt	39264
Ser	Ala	Arg	Thr	Thr	Gln	Thr	Asp	Tyr	Lys	Met	Asp	Met	Val	Gly	Arg	
			585					590					595			
gac	aac	tct	tcc	tgg	gta	caa	ctg	caa	ccg	gga	atc	aat	ata	ggg	gcg	39312
Asp	Asn	Ser	Ser	Trp	Val	Gln	Leu	Gln	Pro	Gly	Ile	Asn	Ile	Gly	Ala	
		600					605					610				
tgg	cgt	gtc	cgc	aat	gcg	acc	agc	tgg	cag	cgg	agt	agt	caa	ctg	tcg	39360
Trp	Arg	Val	Arg	Asn	Ala	Thr	Ser	Trp	Gln	Arg	Ser	Ser	Gln	Leu	Ser	
	615					620					625					
ggg	aag	tgg	cag	gca	gca	tat	acc	tat	gct	gag	cgt	gga	ctg	tac	tca	39408
Gly	Lys	Trp	Gln	Ala	Ala	Tyr	Thr	Tyr	Ala	Glu	Arg	Gly	Leu	Tyr	Ser	
630					635					640					645	
cta	aaa	agt	cgt	ctg	act	ctg	ggg	caa	aag	act	tcg	cag	ggg	gag	ata	39456
Leu	Lys	Ser	Arg	Leu	Thr	Leu	Gly	Gln	Lys	Thr	Ser	Gln	Gly	Glu	Ile	
				650				655						660		
ttt	gat	agt	gtg	cca	ttt	acc	ggg	gtg	atg	ttg	gca	tcg	gat	gac	aac	39504
Phe	Asp	Ser	Val	Pro	Phe	Thr	Gly	Val	Met	Leu	Ala	Ser	Asp	Asp	Asn	

665					670					675						
atg	gtg	ccc	tac	agt	gag	cgg	cag	ttt	gct	ccg	gta	gtg	cgt	ggg	att	39552
Met	Val	Pro	Tyr	Ser	Glu	Arg	Gln	Phe	Ala	Pro	Val	Val	Arg	Gly	Ile	
		680					685					690				
gcc	cgc	acg	cag	gct	cgg	gtg	gag	gtc	aaa	cag	aat	ggg	tac	acc	att	39600
Ala	Arg	Thr	Gln	Ala	Arg	Val	Glu	Val	Lys	Gln	Asn	Gly	Tyr	Thr	Ile	
		695				700					705					
tac	aac	acc	act	gtg	gcg	ccc	gga	ccg	ttt	gca	ctg	cgg	gat	ctg	tcg	39648
Tyr	Asn	Thr	Thr	Val	Ala	Pro	Gly	Pro	Phe	Ala	Leu	Arg	Asp	Leu	Ser	
710					715					720					725	
gta	aca	gac	agt	agt	ggg	gat	ctg	cat	gtc	acc	gtg	tgg	gag	gcc	gat	39696
Val	Thr	Asp	Ser	Ser	Gly	Asp	Leu	His	Val	Thr	Val	Trp	Glu	Ala	Asp	
				730					735					740		
ggc	agt	aca	caa	atg	ttt	gtg	gtg	ccg	tat	cag	acc	ccg	gcg	ata	gca	39744
Gly	Ser	Thr	Gln	Met	Phe	Val	Val	Pro	Tyr	Gln	Thr	Pro	Ala	Ile	Ala	
			745					750					755			
ctg	cac	cag	gga	tat	ttg	aag	tac	agc	ctg	ttg	gcg	ggc	cga	tac	cga	39792
Leu	His	Gln	Gly	Tyr	Leu	Lys	Tyr	Ser	Leu	Leu	Ala	Gly	Arg	Tyr	Arg	
		760					765					770				
tcg	tca	gac	tct	gca	acg	gat	aag	cgg	cag	atc	gcg	cag	gct	acg	ttg	39840
Ser	Ser	Asp	Ser	Ala	Thr	Asp	Lys	Arg	Gln	Ile	Ala	Gln	Ala	Thr	Leu	
		775				780					785					
atg	tat	ggg	ctg	ccg	tgg	aat	ctc	act	gca	tac	ggc	ggg	ata	cag	agt	39888
Met	Tyr	Gly	Leu	Pro	Trp	Asn	Leu	Thr	Ala	Tyr	Gly	Gly	Ile	Gln	Ser	
790					795				800						805	
gca	acg	cat	aat	caa	gct	gca	ttg	ctt	ggg	ttg	ggg	gga	tct	ctc	ggg	39936
Ala	Thr	His	Asn	Gln	Ala	Ala	Leu	Leu	Gly	Leu	Gly	Gly	Ser	Leu	Gly	
				810					815					820		
cgg	tgg	ggg	agt	tta	tct	gtc	gat	gga	agc	gac	aca	cac	agt	cag	cgt	39984
Arg	Trp	Gly	Ser	Leu	Ser	Val	Asp	Gly	Ser	Asp	Thr	His	Ser	Gln	Arg	
			825					830					835			
cag	ggg	gag	gcg	gta	cag	caa	gga	gcc	tcc	tgg	cga	ctg	cgt	tac	agc	40032
Gln	Gly	Glu	Ala	Val	Gln	Gln	Gly	Ala	Ser	Trp	Arg	Leu	Arg	Tyr	Ser	
		840					845					850				
aac	cag	ctg	act	gcg	acg	ggg	aca	aat	ttt	ttt	ctg	acg	aga	tgg	cag	40080
Asn	Gln	Leu	Thr	Ala	Thr	Gly	Thr	Asn	Phe	Phe	Leu	Thr	Arg	Trp	Gln	
		855				860					865					
tat	gcc	tcg	cag	ggc	tat	aac	acc	cta	tcc	gat	gtg	ctc	gac	agt	tat	40128
Tyr	Ala	Ser	Gln	Gly	Tyr	Asn	Thr	Leu	Ser	Asp	Val	Leu	Asp	Ser	Tyr	
870					875					880					885	
cga	cat	aat	ggc	aac	cgt	cta	tgg	tcg	tgg	cgg	gaa	aat	ttg	cag	ccg	40176
Arg	His	Asn	Gly	Asn	Arg	Leu	Trp	Ser	Trp	Arg	Glu	Asn	Leu	Gln	Pro	
				890					895					900		
agc	tcg	cgt	act	acc	ctg	atg	ttg	agt	cag	tca	tgg	ggg	agg	cat	ttg	40224
Ser	Ser	Arg	Thr	Thr	Leu	Met	Leu	Ser	Gln	Ser	Trp	Gly	Arg	His	Leu	
			905				910						915			

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Trp	Thr	Leu	Asp	Phe	Lys	Ala	Cys	Ala	Leu	Ala	Gln	Glu	Asp	Thr	
			1395				1400						1405		
ccgtctgttc	cactcatact	tcctgtatca	gtgaataagg	cgaataactgt	atatcagggt	41775									
cgaggatgta	ttgaaaatct	actcaaggca	aatatgggtta	gcaatcttca	ttgcagaaaa	41835									
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gtttgattca	ctcttttgtg	agcgggggctt	tataagcccc	tgggtataagg	tttgtttatc	42015									
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 acagagtttc attaatacca aaaccaacag gaatggtgtt attacttagc ttcacatgag 45315

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1	5	10	15
Ala Ala Ser Cys Tyr Ala Gly Ser Phe Leu Pro Asn Ser Glu Gln Gln	20	25	30
Lys Ser Val Asp Ile Val Phe Ser Ser Pro Gln Asp Leu Thr Val Ser	35	40	45
Leu Ile Pro Val Ser Gly Leu Lys Ala Gly Lys Asn Ala Pro Ser Ala	50	55	60
Lys Ile Ala Lys Leu Val Val Asn Ser Thr Thr Leu Lys Glu Phe Gly	65	70	75
Val Arg Gly Ile Ser Asn Asn Val Val Asp Ser Thr Gly Thr Ala Trp	85	90	95
Arg Val Ala Gly Lys Asn Thr Gly Lys Glu Ile Gly Val Gly Leu Ser	100	105	110
Ser Asp Ser Leu Arg Arg Ser Asp Ser Thr Glu Lys Trp Asn Gly Val	115	120	125
Asn Trp Met Thr Phe Asn Ser Asn Asp Thr Leu Asp Ile Val Leu Thr	130	135	140
Gly Pro Ala Gln Asn Val Thr Ala Asp Thr Tyr Pro Ile Thr Leu Asp	145	150	155
Val Val Gly Tyr Gln Pro	165		

<210> 3
 <211> 245
 <212> PRT
 <213> Salmonella typhimurium

<400> 3
 Met Lys Ile Val Asn Phe Ala Val Met Ala Val Ala Leu Phe Ala Thr
 1 5 10 15
 Asn Ser Met Val Ser Val Tyr Ala Val Asn Gln Gln Leu Asn Ser Ala
 20 25 30
 Thr Lys Leu Phe Ser Val Lys Leu Gly Ala Thr Arg Val Ile Tyr His
 35 40 45
 Ala Gly Thr Ala Gly Ala Thr Leu Ser Val Ser Asn Pro Gln Asn Tyr
 50 55 60
 Pro Ile Leu Val Gln Ser Ser Val Lys Ala Ala Asp Lys Ser Ser Pro
 65 70 75 80
 Ala Pro Phe Leu Val Met Pro Pro Leu Phe Arg Leu Glu Ala Asn Gln
 85 90 95
 Gln Ser Gln Leu Arg Ile Val Arg Thr Gly Gly Asp Met Pro Thr Asp
 100 105 110
 Arg Glu Thr Leu Gln Trp Val Cys Ile Lys Ala Val Pro Pro Glu Asn

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115	120	125
Glu Pro Ser Asp Thr Gln Ala Lys Gly Ala Thr Leu Asp Leu Asn Leu		
130	135	140
Ser Ile Asn Ala Cys Asp Lys Leu Ile Phe Arg Pro Asp Ala Val Lys		
145	150	155 160
Gly Thr Pro Glu Asp Val Ala Gly Asn Leu Arg Trp Val Glu Thr Gly		
	165	170 175
Asn Lys Leu Lys Val Glu Asn Pro Thr Pro Phe Tyr Met Asn Leu Ala		
	180	185 190
Ser Val Thr Val Gly Gly Lys Pro Ile Thr Gly Leu Glu Tyr Val Pro		
	195	200 205
Pro Phe Ala Asp Lys Thr Leu Asn Met Pro Gly Ser Ala His Gly Asp		
	210	215 220
Ile Glu Trp Arg Val Ile Thr Asp Phe Gly Gly Glu Ser His Pro Phe		
225	230	235 240
His Tyr Val Leu Lys		
	245	

<210> 4
 <211> 836
 <212> PRT
 <213> Salmonella typhimurium

<400> 4
 Met Lys Phe Lys Gln Pro Ala Leu Leu Leu Phe Ile Ala Gly Val Val
 1 5 10 15
 His Cys Ala Asn Ala His Thr Tyr Thr Phe Asp Ala Ser Met Leu Gly
 20 25 30
 Asp Ala Ala Lys Gly Val Asp Met Ser Leu Phe Asn Gln Gly Leu Gln
 35 40 45
 Gln Pro Gly Thr Tyr Arg Val Asp Val Met Val Asn Gly Lys Arg Val
 50 55 60
 Asp Thr Arg Asp Val Val Phe Lys Leu Glu Lys Asp Gly Gln Gly Thr
 65 70 75 80
 Pro Val Leu Ala Pro Cys Leu Thr Val Ser Gln Leu Ser Arg Tyr Gly
 85 90 95
 Val Lys Thr Glu Asp Tyr Pro Gln Leu Trp Lys Ala Ala Lys Pro Pro
 100 105 110
 Asp Glu Cys Ala Asp Leu Thr Ala Ile Pro Gln Ala Lys Ala Val Leu
 115 120 125
 Asp Ile Asn Asn Gln Gln Leu Gln Leu Ser Ile Pro Gln Leu Ala Leu
 130 135 140
 Arg Pro Glu Phe Lys Gly Ile Ala Pro Glu Asp Leu Trp Asp Asp Gly

145		150		155		160
Ile Pro Ala Phe Leu Met Asn Tyr Ser Ala Arg Thr Thr Gln Thr Asp						
		165		170		175
Tyr Lys Met Asp Met Val Gly Arg Asp Asn Ser Ser Trp Val Gln Leu						
		180		185		190
Gln Pro Gly Ile Asn Ile Gly Ala Trp Arg Val Arg Asn Ala Thr Ser						
		195		200		205
Trp Gln Arg Ser Ser Gln Leu Ser Gly Lys Trp Gln Ala Ala Tyr Thr						
		210		215		220
Tyr Ala Glu Arg Gly Leu Tyr Ser Leu Lys Ser Arg Leu Thr Leu Gly						
		225		230		235
Gln Lys Thr Ser Gln Gly Glu Ile Phe Asp Ser Val Pro Phe Thr Gly						
		245		250		255
Val Met Leu Ala Ser Asp Asp Asn Met Val Pro Tyr Ser Glu Arg Gln						
		260		265		270
Phe Ala Pro Val Val Arg Gly Ile Ala Arg Thr Gln Ala Arg Val Glu						
		275		280		285
Val Lys Gln Asn Gly Tyr Thr Ile Tyr Asn Thr Thr Val Ala Pro Gly						
		290		295		300
Pro Phe Ala Leu Arg Asp Leu Ser Val Thr Asp Ser Ser Gly Asp Leu						
		305		310		315
His Val Thr Val Trp Glu Ala Asp Gly Ser Thr Gln Met Phe Val Val						
		325		330		335
Pro Tyr Gln Thr Pro Ala Ile Ala Leu His Gln Gly Tyr Leu Lys Tyr						
		340		345		350
Ser Leu Leu Ala Gly Arg Tyr Arg Ser Ser Asp Ser Ala Thr Asp Lys						
		355		360		365
Arg Gln Ile Ala Gln Ala Thr Leu Met Tyr Gly Leu Pro Trp Asn Leu						
		370		375		380
Thr Ala Tyr Gly Gly Ile Gln Ser Ala Thr His Asn Gln Ala Ala Leu						
		385		390		395
Leu Gly Leu Gly Gly Ser Leu Gly Arg Trp Gly Ser Leu Ser Val Asp						
		405		410		415
Gly Ser Asp Thr His Ser Gln Arg Gln Gly Glu Ala Val Gln Gln Gly						
		420		425		430
Ala Ser Trp Arg Leu Arg Tyr Ser Asn Gln Leu Thr Ala Thr Gly Thr						
		435		440		445
Asn Phe Phe Leu Thr Arg Trp Gln Tyr Ala Ser Gln Gly Tyr Asn Thr						
		450		455		460
Leu Ser Asp Val Leu Asp Ser Tyr Arg His Asn Gly Asn Arg Leu Trp						
		465		470		475
						480

Ser Trp Arg Glu Asn Leu Gln Pro Ser Ser Arg Thr Thr Leu Met Leu
 485 490 495
 Ser Gln Ser Trp Gly Arg His Leu Gly Asn Leu Ser Leu Thr Gly Ser
 500 505 510
 Arg Thr Asp Trp Arg Asn Arg Pro Gly His Asp Asp Ser Tyr Gly Leu
 515 520 525
 Ser Trp Gly Thr Ser Ile Gly Gly Gly Ser Leu Ser Leu Asn Trp Asn
 530 535 540
 Gln Asn Arg Thr Leu Trp Arg Asn Gly Ala His Arg Lys Glu Asn Ile
 545 550 555 560
 Thr Ser Leu Trp Phe Ser Met Pro Leu Ser Arg Trp Thr Gly Asn Asn
 565 570 575
 Val Ser Ala Ser Trp Gln Met Thr Ser Pro Ser His Gly Gly Gln Thr
 580 585 590
 Gln Gln Val Gly Val Asn Gly Glu Ala Phe Ser Gln Gln Leu Asp Trp
 595 600 605
 Glu Val Arg Gln Ser Tyr Arg Ala Asp Ala Pro Pro Gly Gly Gly Asn
 610 615 620
 Asn Ser Ala Leu His Leu Ala Trp Asn Gly Asp Tyr Gly Leu Leu Gly
 625 630 635 640
 Gly Asp Tyr Ser Tyr Ser Arg Ala Met Arg Gln Met Gly Val Asn Ile
 645 650 655
 Ala Gly Gly Ile Val Ile His His His Gly Val Thr Leu Gly Gln Pro
 660 665 670
 Leu Gln Gly Ser Val Ala Leu Val Glu Ala Pro Gly Ala Ser Gly Val
 675 680 685
 Pro Val Gly Gly Trp Pro Gly Val Lys Thr Asp Phe Arg Gly Asp Thr
 690 695 700
 Thr Val Gly Asn Leu Asn Val Tyr Gln Glu Asn Thr Val Ser Leu Asp
 705 710 715 720
 Pro Ser Arg Leu Pro Asp Asp Ala Glu Val Thr Gln Thr Asp Val Arg
 725 730 735
 Val Val Pro Thr Glu Gly Ala Val Val Glu Ala Lys Phe His Thr Arg
 740 745 750
 Ile Gly Ala Arg Ala Leu Met Thr Leu Lys Arg Glu Asp Gly Ser Ala
 755 760 765
 Ile Pro Phe Gly Ala Gln Val Thr Val Asn Gly Gln Asp Gly Ser Ala
 770 775 780
 Ala Leu Val Asp Thr Asp Ser Gln Val Tyr Leu Thr Gly Leu Ala Asp
 785 790 795 800

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Lys Gly Glu Leu Thr Val Lys Trp Gly Ala Gln Gln Cys Arg Val Asn
805 810 815
Tyr Arg Leu Pro Ala His Lys Gly Ile Ala Gly Leu Tyr Gln Met Ser
820 825 830
Gly Leu Cys Arg
835

<210> 5
<211> 156
<212> PRT
<213> Salmonella typhimurium

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Leu Leu Val Ala Ala Ser Ser Leu Val Pro Ile Ala Asn Ala Ala Glu
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Lys Leu Gln Thr Thr Leu Arg Val Gly Thr Tyr Phe Arg Ala Gly His
35 40 45
Val Pro Asp Gly Met Val Leu Ala Gln Gly Trp Val Thr Tyr His Gly
50 55 60
Ser His Ser Gly Phe Arg Val Trp Ser Asp Glu Gln Lys Ala Gly Asn
65 70 75 80
Thr Pro Thr Val Leu Leu Leu Ser Gly Gln Gln Asp Pro Arg His His
85 90 95
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Ile	Pro	Pro	Pro	Gly	Phe	Glu	Ser	Leu	Leu	Glu	Gly	Gln	Thr	Glu	Gln
			20					25					30		
Ile	Glu	Val	Leu	Leu	Pro	Gly	His	Ser	Leu	Gly	Leu	Phe	Pro	Val	Val
		35					40					45			
Val	Lys	Pro	Asp	Thr	Val	Gln	Phe	Met	Ser	Pro	Leu	Met	Val	Leu	Glu
	50					55					60				
Ser	Ser	Gly	Leu	Ala	Ala	Leu	Pro	Ala	Ala	Glu	Arg	Gln	Lys	Ala	Leu
65					70					75					80
Ala	Ala	Leu	Ser	Arg	Pro	Leu	Leu	Arg	Asn	Ser	Asn	Leu	Val	Cys	Gly
				85					90					95	
Val	Ser	Glu	Ala	Lys	Asp	Ser	Ser	Glu	Cys	Gly	Tyr	Val	Ala	Thr	Asp
		100						105					110		
Lys	Glu	Asp	Val	Ala	Val	Ile	Phe	Asp	Glu	Asn	Asn	Ala	Gln	Leu	Ser
		115					120					125			
Leu	Phe	Leu	Asn	Arg	Asp	Trp	Leu	Pro	Asp	Glu	Glu	Arg	Arg	Asp	Lys
		130				135					140				
Arg	Trp	Leu	Thr	Pro	Thr	Pro	Glu	Gly	Val	Ser	Ala	Phe	Ile	His	Arg
145					150					155					160
Gln	Thr	Leu	Tyr	Leu	Ser	Asp	Asp	Leu	His	Ser	Arg	Asn	Met	Thr	Leu
				165					170					175	

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Ser Glu His Lys Glu Ser Ser Leu Trp Leu Leu Ser Lys Asn Arg Ile
820 825 830

Leu Arg Cys Pro Met Ser Val His Lys Arg Arg Asp Val Met Gln Val
835 840 845

Val Gly Asp Val Arg Cys Glu Leu Ser Asp Val Asp Ala Leu Pro Gln
850 855 860

Ala Leu Gln Ile Ser Pro Arg Val Ile Arg Leu Leu Asn Val Ala Gly
865 870 875 880

Leu Leu Arg His Ser Val Gln Glu Ala
885

<210> 5
<211> 359
<212> PRT
<213> Salmonella typhi

<400> 5
Met Ser Asn Lys Met Lys Trp Thr Ser Met Thr Ala His Trp Ser Ala
1 5 10 15

Ile Ile Asn Phe Ile Arg Lys Tyr Val Tyr Pro Ala Arg Ile Ile Ala
20 25 30

Ile Leu Leu Met Ala Gly Ala Thr Leu Pro Gln Val Ala Asp Ala Ile
35 40 45

Thr Val Asp Leu Asn Tyr Asp Lys Asn Asn Val Ala Val Ile Thr Pro
50 55 60

Val Trp Ser Gln Glu Trp Ser Val Ala Asn Val Leu Gly Gly Trp Val
65 70 75 80

Cys Arg Ser Asn Arg Asn Glu Asn Glu Gly Ala Cys Glu Glu Thr His
85 90 95

Leu Val Trp Trp Tyr Ala Phe Gly Ala Tyr Ser Lys Ile Arg Leu Arg
100 105 110

Phe Arg Glu Gln Ile Ser His Ala Glu Ile Thr Leu Ile Leu Leu Gly
115 120 125

Ser Val Arg Asp Ala Cys Tyr Thr Gly Val Ile Asn Met Asn Ala Ala
130 135 140

Ala Cys Gln Trp Gly Arg Ser Leu Lys Leu Arg Ile Pro Ser Glu Glu
145 150 155 160

Leu Ala Lys Ile Pro Thr Ser Gly Thr Trp Lys Ala Thr Leu Val Leu
165 170 175

Asp Tyr Leu Gln Trp Gly Gly Asp Asp Pro Leu Gly Thr Ser Thr Thr
180 185 190

Asp Ile Thr Leu Asn Val Thr Asp His Phe Ala Glu Asn Ala Ala Ile
195 200 205

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Asp	Met	Asn	Asp	Tyr	Tyr	Ser	Phe	Tyr	Glu	Lys	Ile	Ile	Leu	Thr	Asn
		115					120					125			
Ser	Ser	Ile	Ser	Gly	Ser	Ala	Ser	Ser	Phe	Val	Leu	Glu	Gln	Ile	Lys
		130				135					140				
Glu	Thr	Asn	Glu	Leu	Ser	Val									
145					150										